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Publication number:

0 433 662 A2

EUROPEAN PATENT APPLICATION

Application number: 90121904.8

Date of filing: 15.11.90

Int. Cl. 5: C07C 233/07, A61K 31/165,
C07D 295/185, C07D 213/40,
C07D 211/16, C07D 211/22,
C07D 233/18, C07C 233/13,
C07C 233/36, C07C 275/16,
C07C 237/22

No	références, formules, pages à photocopier, etc	No	classement
		1	C07C 233/07
		2	M07C 101:06
		3	inf C07C 295/185/16
		4	inf C07C 233/06
		5	inf C07C 233/18
		6	inf C07C 233/13
		7	inf C07C 233/36
10	p 1, 2, 17, 20-30	8	inf C07C 323/41
11	p 1, 2, 17-30	9	inf C07C 233/47
12	p 1, 2, 18-30	10	inf C07C 317/40
13	p 1, 2, 19-30	11	inf C07C 271/22
		12	inf C07C 237/04
		13	inf C07C 237/22
14	p. 11, 20-25	14	INF. C07D 211/16.
15	p. 11, 20-25	15	INF. C07D 207/08.
16	p. 12, 13, 14, 20-25	16	INF. C07D 213/40B.
17	p. 14, 20-25	17	INF. C07D 239/42B.
18	p. 14, 20-25	18	INF. C07D 279/30.
19	p 13	19	inf C07C 255/29

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(19)



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C07D 233/18, C07C 233/13,
C07C 233/36, C07C 275/16,
C07C 237/22

références, formules, pages à photocopier, etc	No	classement
p 18-19, 21-30	-20	C07 C275/16
p 19, 21-30	-21	C07 C275/30
p 19, 21-30	-22	C07 C327/42

ACAT INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to chemical compounds having pharmacological activity, to pharmaceutical compositions which include these compounds, and to the use of the compounds for the preparation of pharmaceuticals. More particularly, this invention concerns certain novel compounds which inhibit the enzyme acylcoenzyme A: cholesterol acyltransferase (ACAT), pharmaceutical compositions containing these compounds, and the use of the compounds for the preparation of pharmaceuticals useful for treating hypercholesterolemia and atherosclerosis.

In recent years the role which elevated blood plasma levels of cholesterol plays in pathological conditions in man has received much attention. Deposits of cholesterol in the vascular system have been indicated as causative of a variety of pathological conditions including coronary heart disease.

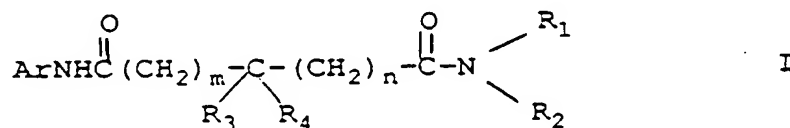
Initially, studies of this problem were directed toward finding therapeutic agents which could be effective in lowering total serum cholesterol levels. It is now known that cholesterol is transported in the blood in the form of complex particles consisting of a core of cholesteryl esters plus triglycerides and an exterior consisting primarily of phospholipids and a variety of types of protein which are recognized by specific receptors. For example, cholesterol is carried to the sites of deposit in blood vessels in the form of low density lipoprotein cholesterol (LDL cholesterol) and away from such sites of deposit by high density lipoprotein cholesterol (HDL cholesterol).

Following these discoveries, the search for therapeutic agents which control serum cholesterol turned to finding compounds which are more selective in their action; that is, agents which are effective in elevating the blood serum levels of HDL cholesterol and/or lowering the levels of LDL cholesterol. While such agents are effective in moderating the levels of serum cholesterol, they have little or no effect on controlling the initial absorption of dietary cholesterol in the body through the intestinal wall.

In intestinal mucosal cells, dietary cholesterol is absorbed as free cholesterol which must be esterified by the action of the enzyme acyl-CoA: cholesterol acyltransferase (ACAT) before it can be packaged into the chylomicrons which are then released into the blood stream. Thus, therapeutic agents which effectively inhibit the action of ACAT prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action.

SUMMARY OF THE INVENTION

The present invention provides a class of compounds which have acyl-CoA: cholesterol acyltransferase (ACAT) inhibitory activity and intermediates useful in preparing said compounds having the following structure:



wherein Ar is

(a) phenyl(CH₂)_x- wherein x is zero to 2 and wherein the phenyl ring is unsubstituted or is substituted with from 1 to 3 substituents selected from

alkyl having from 1 to 6 carbon atoms and which is straight or branched,

alkoxy having from 1 to 6 carbon atoms and which is straight or branched,

phenoxy,

hydroxy,

fluorine,

chlorine,

bromine,

(9)



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C07D 233/18, C07C 233/13,
C07C 233/36, C07C 275/16,
C07C 237/22

(30) Priority: 16.11.89 US 437727
09.10.90 US 594484

(43) Date of publication of application:
26.06.91 Bulletin 91/26

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

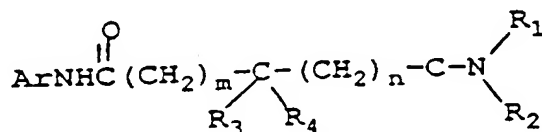
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(54) **Acat inhibitors.**

(57) The invention is novel compounds having acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitory activity of the formula I



(I),

The invention further comprises a process for the preparation of compounds of the formula I, pharmaceutical compositions containing them and the use of compounds (I) for the preparation of pharmaceutical compositions useful for treating hypercholesterolemia and atherosclerosis.

- nitro,
 trifluoromethyl,
 -COOH,
 -COOalkyl wherein alkyl has from 1 to 4 carbon atoms,
 5 -NR₅R₆ wherein
 R₅ and R₆ are independently hydrogen or alkyl of from 1 to 4 carbon atoms;
 (b) 1- or 2-naphthyl which is unsubstituted or substituted with
 alkyl having from 1 to 6 carbon atoms and which is straight or branched;
 alkoxy having from 1 to 6 carbon atoms and which is straight or branched,
 10 hydroxy,
 fluorine,
 chlorine,
 bromine,
 nitro,
 15 trifluoromethyl,
 -COOH,
 -COOalkyl wherein alkyl has from 1 to 4 carbon atoms,
 -NR₅R₆ wherein R₅ and R₆ have the meanings defined above;
 wherein each of m and n is independently zero, one, or two;
 20 wherein each of R₃ and R₄ is independently
 (a) hydrogen;
 (b) a straight or branched alkyl group having from 1 to 10 carbon atoms;
 (c) a straight chain alkyl group having from 1 to 10 carbon atoms wherein the terminal carbon atom is
 substituted with hydroxy or NR₅R₆ wherein R₅ and R₆ have the meanings defined above; or
 25 (d) R₃ is hydrogen and R₄ is the group -NHR₁₀ wherein R₁₀ is -C(=O)alkyl C₁₋₆ wherein the alkyl moiety
 is straight or branched; -(C=O)O-t-C₄H₉; -C(=O)OCH₂C₆H₅;



wherein X is oxygen or sulfur and the alkyl moiety is straight or branched;



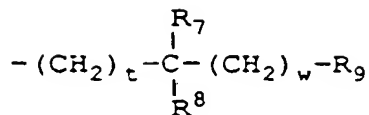
wherein X is oxygen or sulfur and Ph is phenyl or substituted phenyl wherein the substituents vary in
 40 number from 1 to 3 and are selected from chlorine, fluorine, bromine, iodine, trifluoromethyl, lower alkyl
 having from 1 to 4 carbon atoms and being straight or branched, lower alkoxy having from 1 to 4 carbon
 atoms and being straight or branched or NR₅R₆ wherein R₅ and R₆ have the meanings defined
 hereinabove; or



wherein Ph is phenyl or phenyl substituted with from 1 to 3 substituents selected from chlorine, fluorine,
 50 bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched,
 lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR₅R₆ wherein R₅ and R₆
 have the meanings defined hereinabove; or
 (e) R₃ is hydrogen and R₄ is NR₁₂R₁₃ wherein each of R₁₂ and R₁₃ is selected from hydrogen, straight or
 branched alkyl having from 1 to 6 carbon atoms, phenyl or benzyl or phenyl or benzyl substituted on any
 positions 2 through 6 of the aromatic ring with from 1 to 3 substituents selected from fluorine, chlorine,
 55 bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched,
 lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR₅R₆ wherein R₅ and R₆
 have the meanings defined hereinabove;
 wherein each of R₁ and R₂ is independently

- (a) hydrogen,
(b) the group

5



- 10 wherein t is zero to 4; w is zero to 4 with the proviso that the sum of t and w is not greater than 5; R₇ and R₈ are independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R₇ is hydrogen, R₈ can be selected from the group defined for R₉; and R₉ is phenyl or phenyl substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 6 carbon atoms, straight or branched alkoxy having from 1 to 6 carbon atoms, the group

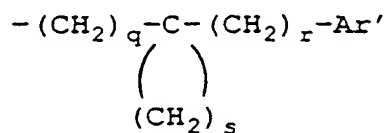
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- alkyl wherein e is zero, one or two, and alkyl is straight or branched and has from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or -NR₅R₆ wherein R₅ and R₆ have the meanings defined above;
(c) the group

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- wherein q is zero to 3; r is zero to 2; s is 2 to 6; and Ar' is phenyl,

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- 1- or 2-naphthyl,
phenyl or 1- or 2-naphthyl substituted with alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
hydroxy,
benzyloxy,
40 fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,
45 -NH-COCH₃,
-CONH₂,
-COOH,
-COOalkyl wherein alkyl has from one to four carbon atoms,
-CH₂COOH,
50 -CH₂CONH₂,
-NR₅R₆ wherein R₅ and R₆ have the meanings defined above;

- (d) a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds;

- (e) an alkyl group having from 1 to 6 carbon atoms wherein the terminal carbon is substituted with hydroxy,
55 -NR₅R₆ wherein R₅ and R₆ have the meanings defined above, or -COOalkyl wherein alkyl is straight or branched and has from 1 to 4 carbon atoms;

- (f) -(CH₂)_pQ wherein p is a number from zero to 3 and Q is a 5- or 6-membered monocyclic or fused bicyclic heterocycle containing at least 1 to 4 nitrogen, oxygen, or sulfur atoms in at least one ring member;

- (g) phenyl or phenyl substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 6 carbon atoms, alkoxy which is straight or branched and has from 1 to 6 carbon atoms, alkylthio which is straight or branched and has from 1 to 6 carbon atoms, alkylthio which is straight or branched and has from 1 to 6 carbon atoms, $-NR_5R_6$ wherein R_5 and R_6 have the meanings defined above, hydroxy, nitro, chlorine, fluorine, bromine, or trifluoromethyl; or
- (h) NR_1R_2 taken together are phenothiazine or form a monocyclic heterocyclic group selected from pyrrolidino, piperidino, morpholino, or piperazino, each of which is unsubstituted or is substituted with one substituent selected from benzhydryl, straight or branched alkyl having from 1 to 6 carbon atoms, ω -hydroxyalkyl having from 1 to 6 carbon atoms, phenyl, benzyl, or substituted phenyl or substituted benzyl wherein the substituents vary from 1 to 3 and can be on any position of 2 through 6 of the aromatic ring and are selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro; or a pharmaceutically acceptable salt thereof.

This invention also provides pharmaceutical compositions containing the compounds of Formula I and the use of the compounds for the preparation of pharmaceuticals useful for treating hypercholesterolemia and atherosclerosis. The compounds of Formula I wherein R_1 and R_2 are both hydrogen are useful as intermediates in preparing pharmaceutically active compounds of the invention. All the other compounds of Formula I are ACAT inhibitors.

DETAILED DESCRIPTION OF INVENTION

The compounds of the present invention provide a novel class of diamides which are ACAT inhibitors rendering them useful in treating hypercholesterolemia and atherosclerosis.

- Illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, iso-butyl, *n*-pentyl, isopentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-undecyl, *n*-dodecyl, *n*-hexadecyl, 2,2-dimethyldodecyl, 2-ethyltetradecyl, and *n*-octadecyl groups.

- Illustrative examples of straight or branched hydrocarbon chains having from 1 to 20 carbon atoms and having from 1 to 3 double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

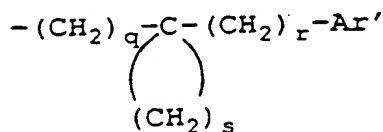
Straight or branched alkoxy groups having from 1 to 6 carbon atoms include, for example, methoxy, ethoxy, *n*-propoxy, *t*-butoxy, and pentyloxy.

- The term alkylthio having from 1 to 6 carbon atoms means the group $C_{1-6}alkyl-S-$ wherein the alkyl moiety is straight or branched.

- A 5- or 6-membered monocyclic or fused bicyclic heterocycle is a monocyclic or fused bicyclic aromatic ring containing at least 1 to 4 heteroatoms in at least one ring, such as nitrogen, oxygen, or sulfur or a combination thereof. Such a heterocyclic group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl, or N-oxides of heterocycle containing a nitrogen atom.

- More specifically, such a heterocycle may be a 2- or 3-thienyl; 2- or 3-furanyl; 2-, or 3-, or 4-pyridyl or -pyridyl-N-oxide; 2-, 4-, or 5-pyrimidinyl; 3- or 4-pyridazinyl; 2-pyrazinyl; 2-pyrazinyl-N-oxide; 2- or 3-pyrrolyl; 3-, 4-, or 5-pyrazolyl; 3-, 4-, or 5-oxazolyl; 3-, 4-, or 5-isoxazolyl; 3-, 4-, or 5-oxazolyl; 3-, 4-, or 5-isothiazolyl; 5-tetrazolyl; 3- or 5-(1,2,4-)triazolyl; 4- or 5-(1,2,3-)triazolyl; 2-, 4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; or 2-, 3-, 4-, 5-, 6-, or 7-benzothieryl.

- Preferred compounds of this invention are those wherein Ar is phenyl or Ar' is phenyl or substituted phenyl and more preferably wherein Ar' is phenyl substituted on the 2,6-positions. Other preferred compounds of this invention are those wherein R_1 or R_2 represents the group

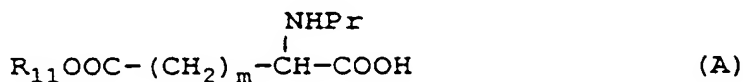


appropriate acid halide, e.g., the acid chloride (2) in an aprotic, nonpolar solvent such as ethyl acetate, tetrahydrofuran, diethyl ether, or methylene chloride in the presence of a tertiary amine such as triethylamine, diisopropyl ethylamine or pyridine for about 1 to 24 hours at a temperature of from about 0° to 25° C to give the amide (3). The amide (3) is converted to the free acid (4) by treatment with a mild aqueous base, e.g., sodium hydroxide in a lower alcohol such as methanol or ethanol at a temperature of from 25°-80° C for from about 1 to 20 hours. The free acid can be converted to the bis-amide (5) by various means and essentially by any means which affords an activated ester to which is added an appropriate amine of the formula NHR_1R_2 wherein R_1 and R_2 have the meanings defined in Formula I. For example, the acid (4) can be treated with a carbodiimide such as dicyclohexyl carbodiimide in methylene chloride and reacted with the amine at a temperature varying from about 0° to 25° C. Alternatively, the acid (4) can be treated with a chloroformate such as methyl, ethyl, or isobutyl chloroformate in the presence of a tertiary amine, e.g., triethylamine, to give a mixed anhydride which is then reacted with an amine of the formula NHR_1R_2 . Additionally, the acid (4) can be treated with carbonyldiimidazole and reacted with an appropriate amine or the acid (4) can be converted to the corresponding acid chloride by treatment with thionyl chloride or oxalyl chloride/dimethylformamide, and reacted with an appropriate amine of the formula NHR_1R_2 in the presence of base. The amines, NHR_1R_2 , are commercially available or are prepared by procedures well known in the art.

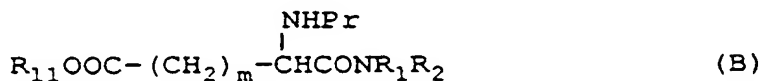
The compounds of this invention wherein R_4 is other than the group $-\text{NHR}_{10}$ can also be prepared as set forth in Chart II whereby an appropriate aryl amine (1) is reacted with an acid anhydride (6) in an aprotic nonpolar solvent to give the acid (4) which is then converted to the bis-amide as described above. It should be recognized that in the scheme of Chart II the addition of the amine groups could be reversed. That is, the acid anhydride could first be reacted with the amine NHR_1R_2 to give a compound of formula (7) set forth in Chart I which could then be converted to compounds (5) by treating compounds (7) in a manner as described above to afford an activated ester to which is added an appropriate aryl amine of the formula ArNH_2 .

Further, the compounds of Formula I wherein R_3 and R_4 are other than hydrogen can be prepared from the corresponding compounds wherein R_3 and R_4 are hydrogen by treatment with a mild base such as sodium hydride or sodium carbonate/dimethylformamide and alkylating with an appropriate alkylhalide of the formula R_3halide or R_4halide wherein R_3 and R_4 have the same meaning as defined in Formula I but are not hydrogen, and halide is a halogen-atom, e.g., chloride.

The compounds of this invention wherein R_3 is hydrogen and R_4 is the group $-\text{NHR}_{10}$ or $-\text{NR}_{12}\text{R}_{13}$ are prepared by reacting a compound of the formula



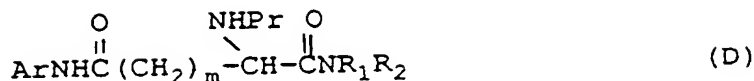
wherein R_{11} is a lower alkyl C_{1-4} , m is zero, one or two and Pr is a protecting group such as the tert-butyloxycarbonyl or benzyloxycarbonyl with a carbodiimide such as dicyclohexylcarbodiimide followed by addition of an amine of the formula NHR_1R_2 wherein R_1 and R_2 have the meanings defined hereinabove at a temperature varying from about 0° C to 25° C. The resulting amide ester



is then converted to the amide acid by mild base hydrolysis to give compounds of the formula

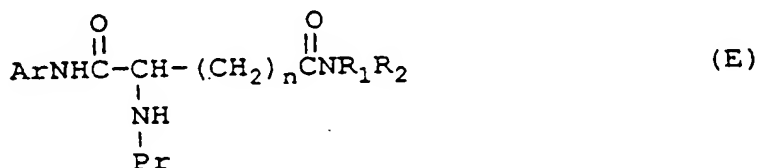


which are treated with a carbodiimide as generally described above followed by addition of an appropriate aryl amine of the formula ArNH_2 wherein Ar has the meaning defined above to give compounds



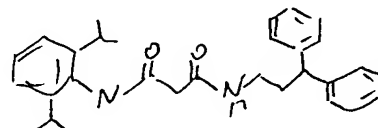
5 If desired, the protecting group can be removed to give compounds of Formula I wherein R₃ is hydrogen and R₄ is the group -NR₁₂R₁₃ wherein R₁₂ and R₁₃ are hydrogen. The latter compounds can be acylated by generally known procedures, e.g., by reaction with an appropriate acid chloride or isocyanate or thioisocyanate to give compounds of Formula I wherein R₃ is hydrogen and R₄ is NHR₁₀ or the latter
 10 compounds can be alkylated by procedures generally known in the art to give compounds of Formula I wherein R₃ is hydrogen and R₄ is NR₁₂R₁₃ wherein R₁₂ and R₁₃ are both not hydrogen.

It is apparent from the foregoing that compounds of the following formula (E) wherein n is zero, one or two can be obtained by following the above general procedure, only reversing the order of the amine
 15 additions.



25 The compounds of Formula (A) are commercially available or are obtained from a corresponding diester derivative.

EXAMPLE 1



30 N-[2,6-Bis(1-methylethyl)phenyl]-N'-(2,2-diphenylethyl)propanediamide

(a) To a mixture of 43.30 g (0.24 mole) of 2,6-diisopropylaniline and excess triethylamine in 400 mL of ethyl acetate was added dropwise 36.7 g (0.24 mole) of ethyl malonylchloride (technical) at 0 °C; more ethyl
 35 acetate was added as the reaction mixture became a slurry. The reaction mixture was stirred for 1 hour at 0 °C then allowed to sit at room temperature for 30 minutes. The resulting white precipitate was filtered off and concentrated on a rotary evaporator, leaving an oil which crystallized. Hexane was added to the crystalline material and the solid collected by filtration to give 3-[[2,6-bis(1-methylethyl)phenyl]amino]-3-oxopropionic acid ethyl ester.

(b) To 4.6 g (0.016 mole) of the ethyl ester obtained above in 50 mL MeOH was added 17 mL 1M NaOH at room temperature, after which water was added until the solution became cloudy. The solution
 40 was allowed to sit at room temperature for 2 hours then concentrated on a rotary evaporator, diluted with H₂O and EtOAc and made acidic with 1N HCl. Brine was added and the layers were separated, the organic layer was washed with brine, dried over MgSO₄, filtered, and stripped to a white flaky solid. The solid was recrystallized from hexane to give 3-[[2-bis(2-methyl)phenyl]amino]-3-oxopropionic acid.

(c) To a mixture of 0.52 g (0.002 mole) of the above-obtained acid and 0.40 g (0.002 mole) of 2,2-diphenylethylamine in 25 mL CH₂Cl₂ was added 0.41 g (0.002 mole) of dicyclohexylcarbodiimide at room
 50 temperature. The reaction mixture was allowed to stand 4 days at room temperature, then was diluted with EtOAc, washed with H₃PO₄ and brine, dried over MgSO₄, filtered, and concentrated to a viscous oil/glass. The concentrate was recrystallized from ethyl acetate and ethyl acetate/hexane (50:50) to give the title compound.

IR-IB 890914; MS-MB 891126; NBR-ND 893682.

Calc.:	C, 78.70;	H, 7.74;	N, 6.33.
Found:	C, 78.42;	H, 7.74;	N, 6.30.

When in the procedure of Example 1(c) an appropriate amount of the amine set forth in the following Table 3 is substituted for 2,2-diphenylethylamine, the respective product listed in Table 3 is obtained:

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TABLE 3

5	Amine	Product
10	1-phenylcyclopentyl-methyl amine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-(1-phenylcyclopentyl)methylpropanediamide; IR (KBr) 3278, 2962, 1670, 1653, 1628, 1497 cm^{-1} .
15	diphenylmethylamine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-(diphenylmethyl)-propanediamide; IR (KBr) 3262, 1664, 1644, 1521, 699 cm^{-1} .
20	N,N-di(phenylmethyl)amine	N'-[2,6-bis(1-methylethyl)-phenyl]-N,N-bis(phenylmethyl)-propanediamide; IR (KBr) 3224, 2962, 1674, 1614, 1533, 1449, 703 cm^{-1} .
25	N-diphenylmethyl-N-(1-methylethyl)amine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-(diphenylmethyl)-N-(1-methylethyl)propanediamide; IR (KBr) 3280, 2964, 1676, 1627, 708 cm^{-1} .
30	N-phenylpiperazino	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-4-phenyl-1-piperazinepropanamide; IR (KBr) 3216, 2961, 1684, 1628, 1506, 1459, 1230, 758 cm^{-1} .
35	4-phenylpiperidino	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-4-phenyl-1-piperidinepropanamide; IR (KBr) 2965, 1660, 1645, 1496, 1445, 1214, 699 cm^{-1} .
40	2-hydroxymethyl-pyrrolidino	(S)-N-[2,6-bis(1-methylethyl)phenyl]-2-(hydroxymethyl)- β -oxo-1-pyrrolidinepropanamide; IR (KBr) 3371, 3248, 1640, 1534, 1451, 1067 cm^{-1} .
45	N-phenylmethyl-N-(1-methylethyl)amino	N'-[2,6-bis(1-methylethyl)-phenyl]-N-(1-methylethyl)-N-(phenylmethyl)propanediamide; IR (KBr) 3245, 2961, 1682, 1618, 1607, 1533, 1449, 716 cm^{-1} .
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TABLE 3

	Amine	Product	
5			
10	N-(2-pyridylethyl)- N-methylamine	N'-[2,6-bis(1-methylethyl)- phenyl]-N-methyl-N-[2-(2- pyridyl)ethyl]propanediamide; IR (KBr) 3294, 2963, 1666, 1652, 1644, 1509, 1434, 748 cm ⁻¹ .	UV
15	N,N-dipentylamine	N,N-dipentyl-N'-[2,6-bis(1- methylethyl)phenyl]propane- diamide	
20	phenylmethylamine	N-[2,6-bis(1-methylethyl)- phenyl]-N'-(phenylmethyl)- propanediamide; IR (KBr) 3316, 3234, 1650, 1546, 1528, 1256, 746 cm ⁻¹ .	233/06
25	N,N-di-(2-hydroxy- ethyl) amine	N,N-di-(2-hydroxyethyl)-N'- [2,6-bis(1-methylethyl)- phenyl]propanediamide; IR (KBr) 3410, 3252, 3245, 1655, 1634, 1363, 624 cm ⁻¹ .	233/18
30	N-(4-fluorophenyl- methyl)-N-(1-methyl- ethyl) amine	N'-[2,6-bis(1-methylethyl)- phenyl]-N-[(4-fluorophenyl)- methyl]-N-(1-methylethyl)- propanediamide; IR (KBr) 3293, 1671, 1630, 1512, 1223, 797 cm ⁻¹ .	233/13
35	N-(2-dimethylamino- ethyl)-N-phenyl- methylamine	N-[2,6-bis(1-methylethyl)- phenyl]-N'-(2-dimethyl- aminoethyl)-N'-(phenyl- methyl)propanediamide; IR (KBr) 3185, 2964, 1623, 1609, 1531, 1459, 703 cm ⁻¹ .	233/36
40			
45	N-(2-hydroxyethyl-N- phenylmethylamine	N-[2,6-bis(1-methylethyl)- phenyl]-N'-(2-hydroxyethyl)- N'-(phenylmethyl)propane- diamide; IR (KBr) 3249, 2964, 1654, 1627, 1533, 700 cm ⁻¹ .	233/18
50	N-ethyl-N-(2- diethylaminoethyl)- amine	N-[2,6-bis(1-methylethyl)- phenyl]-N'-(ethyl)-N'-(2- diethylaminoethyl)propane- diamide; IR (Q film) 3243, 2937, 2931, 1685, 1670, 1624, 1203, 785 cm ⁻¹ .	233/36
55			

TABLE 3

	Amine	Product	
5			
10	N-(2-hydroxyethyl)-piperazine	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-4-(2-hydroxyethyl)-1-piperazine-propanamide; IR (KBr) 3426, 2961, 1638, 1525, 1054, 733 cm^{-1} .	295/18 B'G
15	morpholine	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-1-morpholine-propanamide; IR (KBr) 3235, 1669, 1529, 1440, 1224, 798 cm^{-1} .	4
20	thiomorpholine	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-1-thiomorpholinepropanamide; IR (KBr) 3439, 1654, 1467, 1343, 961, 796 cm^{-1} .	
25	N-(2-cyanoethyl)-N-(phenylmethyl)amine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-(2-cyanoethyl)-N'-(phenylmethyl)propanediamide; IR (KBr) 3259, 2969, 1642, 1533, 1335, 742 cm^{-1} .	255/29
30	isopropylphenylamine	N'-(2,6-bis(1-methylethyl)-phenyl)-N-(1-methylethyl)-N-phenylpropanediamide; IR (KBr) 3261, 2966, 1645, 1629, 1538, 1531, 1522, 1353, 703 cm^{-1} .	
35	isopropyl-2-pyridylmethylamine	N-[2,6-bis(1-methylethyl)-phenyl]-N-(1-methylethyl)-N-[(3-pyridinyl)methyl]propanediamide; IR (KBr) 2967, 1666, 1630, 1539, 1413, 971, 713 cm^{-1} .	UW
40			
45	N-benzylpiperazine	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-4-(phenylmethyl)-1-piperazine-propanamide; IR (KBr) 3263, 2961, 1684, 1618, 1521, 1457, 1000, 699 cm^{-1} .	290145/18 B
50	diphenylamine	N'-(2,6-bis(1-methylethyl)-phenyl)-N,N-diphenylpropanediamide; IR KBR 3243, 1661, 1646, 1540, 1349, 695 cm^{-1} .	
55			

TABLE 3

	Amine	Product	
5			
10	isopropyl-4-methyl-thiophenylamine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-(1-methylethyl)-N-[[4-(methylthio)phenyl]-methyl]propanediamide; IR (KBr) 3248, 2965, 1684, 1601, 1331, 799 cm^{-1} .	383/41
15	phenylaminoacetic acid, ethyl ester	N-[3-[[2,6-bis(1-methylethyl)-phenyl]amino]-1,3-dioxo-propyl]-N-phenylglycine, ethyl ester; IR (KBr) 3238, 1738, 1646, 1389, 1208, 763 cm^{-1} .	233/47
20	N-(2-methoxyphenyl)-piperazine	N-[2,6-bis(1,1-dimethylethyl)-phenyl]-4-(2-methoxyphenyl)- β -oxo-1-piperazinepropanamide; IR (KBr) 3265, 1654, 1629, 1489, 1040, 935 cm^{-1} .	225/18
25	N-benzhydryl-piperazine	N-[2,6-bis(1-methylethyl)-phenyl]-1-(diphenylmethyl)-1-piperazinepropanamide; IR (KBr) 3391, 3291, 2963, 1634, 1452, 796, 706 cm^{-1} .	
30	4-methoxybenzyl-2-pyridylamine	N-[2,6-bis(1-methylethyl)-phenyl]- β -[[4-methoxyphenyl]-methyl](2-pyridinyl)amino]- β -oxopropanamide; IR (KBr) 3254, 3248, 2931, 1654, 1467, 1250, 799 cm^{-1} .	VW
35			
40	phenothiazine	N-[2,6-bis(1-methylethyl)-phenyl]- β -oxo-10H-phenothiazine-10-propanamide; IR (KBr) 3330, 2963, 1654, 1474, 1344, 739 cm^{-1} .	"
45	4-methoxyphenyl-2-pyrimidinylamine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-[(4-methoxyphenyl)-methyl]-N-(2-pyrimidinyl)-propanediamide; IR (KBr) 3298, 3238, 2962, 1669, 1514, 1414, 808 cm^{-1} .	"
50	heptylamine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-heptylpropane-diamide; IR (KBr) 3327, 3273, 1671, 1523, 1443, 748 cm^{-1} .	133
55			

TABLE 3

	Amine	Product
5	2,6-diisopropyl-phenylamine	N,N'-bis[2,6-bis(1-methylethyl)phenyl]propanediamide; IR (KBr) 3233, 1648, 1520, 1257, 715 cm ⁻¹ .
10	(4-dimethylamino-benzyl)(isopropyl)-amine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-[[4-(dimethylamino)-phenyl]methyl]-N-(1-methylethyl)propanediamide; IR (KBr) 3262, 2963, 1617, 1525, 1447, 1346, 1069, 743 cm ⁻¹ .
15	1,1,3,3-tetramethyl-butylamine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-(1,1,3,3-tetramethylbutyl)propanediamide; IR (KBr) 3438, 3297, 2936, 1653, 1540, 1473, 1230 cm ⁻¹ .
20	(methyl(octyl)amine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-methyl-N-octylpropanediamide; IR (KBr) 3284, 3263, 2927, 1654, 1508, 1129, 717 cm ⁻¹ .
25	1,1-dimethyl-2-phenylethylamine	N-[2,6-bis(1-methylethyl)-phenyl]-N'-(1,1-dimethyl-2-phenylethyl)propanediamide; IR (KBr) 3297, 2964, 1643, 1559, 1457, 1364, 702 cm ⁻¹ .
30	2,6-bis(dimethyl-amino)benzylamine	N-[2,6-bis(dimethylamino)-phenyl]-2,6-bis(1-methylethyl)phenyl]propanediamide; IR (KBr) 3462, 3243, 1658, 1507, 1324, 727 cm ⁻¹ .
35	(methyl)(octadecyl)-amine	N'-[2,6-bis(1-methylethyl)-phenyl]-N-methyl-N-octadecylpropanediamide; IR (KBr) 3297, 2961, 2923, 1653, 1629, 1512, 1406, 719 cm ⁻¹ .
40		
45		
50		
55		

Following the general procedure of Example 6, only substituting an appropriate amount of pyridine-3-carboxaldehyde or 4-dimethylaminobenzaldehyde for 4-thiomethylbenzaldehyde, the following respective amines were obtained: N-(1-methylethyl)-3-pyridinemethanamine and 4-(dimethylamino)-N-(1-methylethyl)-benzenemethanamine.

EXAMPLE 2

N-(1-Methylethyl)diphenylmethanamine

A mixture of 9.88 g (0.04 mole) of benzhydryl bromide, 2.4 g (0.04 mole) of isopropyl amine, and excess triethylamine in 300 mL of ethyl acetate was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, after which more triethylamine was added and the reaction mixture was heated on a steambath. Excess concentrated HCl was added, then the mixture was washed with ethyl acetate, made basic with sodium hydroxide, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the title compound as an oil.

EXAMPLE 3

N-[2,6-Bis(1-methylethyl)phenyl]-N'-(diphenylmethyl)pentanediamide

(a) A mixture of 3.34 g (0.02 mole) 2,6-diisopropyl aniline and 2.31 g (0.02 mole) glutaric anhydride in 50 mL EtOAc was heated on the steambath overnight then allowed to sit 3 days and nights at room temperature. The mixture was taken up in EtOAc, washed with 1N HCl and brine, dried over MgSO_4 , filtered, and stripped to a viscous oil. Addition of 1/1 hexane/EtOAc caused precipitation of white crystals to give 4-[2,6-bis(1-methylethyl)phenylaminocarbonyl]butyric acid.

(b) To a mixture of 0.58 g (0.002 mole) of the above obtained acid, 0.40 g (0.0022 mole) benzhydryl amine, and 100 mL CH_2Cl_2 was added all at once 0.44 g (0.0021 mole) of dicyclohexylcarbodiimide at 0° C. Stirring was continued and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was allowed to sit 2 days at room temperature, filtered, and concentrated in vacuo. The concentrate was taken up in CH_2Cl_2 and filtered through SiO_2 (70-250) using CH_2Cl_2 as eluant to give the title compound. IR (KBr) 3262, 1655, 1638, 1524, 697 cm^{-1} .

EXAMPLE 4

4-[2,2-Diphenylethyl]aminocarbonyl]butyric acid

A mixture of 0.99 g (0.005 mole) 2,2-diphenylethylamine, 0.58 g (0.005 mole) glutaric anhydride, and 50 mL EtOAc was heated on the steambath until solution occurred. The solution was concentrated in vacuo to an oil, which was filtered through SiO_2 (70-250) using EtOAc as eluant to give the title compound.

When in the procedure of Example 4 an appropriate amount of benzhydrylamine or dibenzylamine is substituted for 2,2-diphenylethylamine, the following respective acids were obtained:

4-[[[diphenylmethyl]amino]carbonyl]butyric acid.

4-[[[N,N-bis(phenylmethyl)amino]carbonyl]butyric acid.

EXAMPLE 5

3-[2(2,2-Diphenylethyl)aminocarbonyl]propionic acid

A mixture of 0.99 g (0.005 mole) 2,2-diphenylethylamine and 0.50 g (0.005 mole) succinic anhydride in 50 mL EtOAc was heated until solution occurred. The solution was allowed to sit overnight at room temperature, then concentrated in vacuo. The concentrate was taken up in EtOAc and hexane, and the resulting solid collected by filtration. The solid was washed with EtOAc to give the title compound.

When in the procedure of Example 5 an appropriate amount of diphenylmethanamine or dibenzylamine

is substituted for 2,2-diphenylethylamine the following acids were obtained:
 3-[(diphenylmethyl)aminocarbonyl]propionic acid.
 3-[[N,N-bis(phenylmethyl)amino]carbonyl]propionic acid.

EXAMPLE 6

N-(1-Methylethyl)-4-(methylthio)benzenemethanamine

4-Thiomethylbenzaldehyde (15.3 g, 100 mmole) and isopropylamine (8.0 g, 140 mmole) were mixed together in 200 mL methanol with about 40 g of calcium sulfate as the drying agent. The mixture was stirred overnight at room temperature after which 3.9 g of sodium borohydride was added over one-half hour. The reaction mixture was stirred overnight at room temperature then filtered through filter cell. The filtrate was concentrated to dryness, and the resulting residue was partitioned between 150 mL 1N sodium hydroxide and ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and stripped to a clean oil to give the title compound. IR (KBr) 3248, 1684, 1601, 1522, 1331, 799 cm^{-1} .

EXAMPLE 7

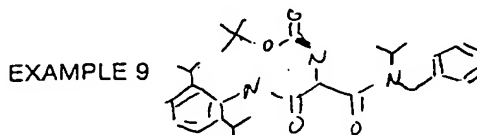
N'-[2,6-Bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-[[4-(methylsulfinyl)phenyl]methyl]propanediamide *CH₃S⁺*

N'-[2,6-Bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-[[4-(methylthio)phenyl]methyl]propanediamide (1.40 g, 3.2 mmole) and metachloroperbenzoic acid (0.69 g, 80%) were stirred overnight at room temperature. The reaction mixture was concentrated to dryness, taken up in ethyl acetate, washed with aqueous NaHSO_3 , aqueous K_2CO_3 , and aqueous NaCl , dried (MgSO_4), and concentrated. The product was purified by filtration through SiO_2 (70-230 mesh) using ethyl acetate as eluant. The product was obtained as a white foam. 0.51 g, 35%. IR (KBr) 3253, 2965, 1677, 1637, 1521, 799 cm^{-1} .

EXAMPLE 8

N'-[2,6-Bis(1-methylethyl)phenyl]-2,2-dimethyl-N-(1-methylethyl)-N-(phenylmethyl)propanediamide

Oxalyl chloride (50 mL) was added to 5.0 g dimethylmalonic acid and a few drops DMF at room temperature. Reaction was immediate. The excess oxalyl chloride was removed on the rotary evaporator, leaving behind a mobile yellow oil. This oil was added to a mixture of 6.7 g 2,6-diisopropylaniline, 5.6 g N-benzyl isopropylamine, and excess triethylamine in 250 mL ethyl acetate at room temperature. The reaction mixture was concentrated to dryness after sitting 30 minutes at room temperature. The residue was taken up in ethyl acetate and concentrated again on the rotary evaporator. The residue was taken up in ethyl acetate, washed with 200 mL 1N HCl and brine, dried over MgSO_4 , filtered, and concentrated to a brown oil. Attempted crystallization from hexane and 1/1 hexane/EtOAc gave only impure product. The brown oil was then filtered through silica gel (70-230 mesh) using 1/1 hexane/EtOAc as eluant to give the product as an oil. The oil was crystallized from diethyl ether. 1.66 g, 10.4%. IR (KBr) 3335, 2967, 1670, 1624, 1497 cm^{-1} .



(±) [1-[[[2,6-Bis(1-methylethyl)phenyl]amino]carbonyl]-2-[[1-(1-methylethyl)(phenylmethyl)amino]-2-oxoethyl]-carbamic acid, 1,1-dimethylethyl ester

(a) A solution of 31.7 g (150 mmole) of diethyl aminomalonate hydrochloride in 400 mL 1/1 THF/ H_2O was cooled to 0°C and 20 mL triethylamine was added followed by 35 g di-t-butylidicarbonate. The reaction mixture was stirred 1.25 hours at 0°C and was then warmed briefly to 50°C. The reaction mixture was stirred overnight at room temperature, concentrated to remove THF, diluted with ethyl acetate, washed with 200 mL 10% citric acid solution and brine, dried (MgSO_4), filtered, and concentrated to a clear viscous

liquid to give N-[bis(ethoxycarbonyl)methyl]carbamic acid, 1,1-dimethylethyl ester. 43.3 g, 100%. IR (LF) 2938, 1761, 1720, 1506, 1370, 1163, 780 cm^{-1} .

(b) The ester obtained in (a) above (11.02 g, 40 mmole) in 30 mL ethanol was mixed with 40 mL 1N NaOH and then heated gently (40 °C) while slowly removing the solvent on the rotary evaporator. Water was added and the mixture was concentrated to a viscous oil. The oil was taken up in H₂O and allowed to sit overnight at room temperature. The aqueous solution was diluted with H₂O, made acidic with 10% citric acid solution, and extracted twice with diethyl ether. The ether solution was dried (MgSO₄), filtered, and concentrated to give the N-[(carboxy)(ethoxycarbonyl)methyl]carbamic acid, 1,1-dimethylethyl ester as an oil (9.19 g, 92.8%), which crystallized on standing. IR (KBr) 3288, 2985, 1767, 1757, 1665, 1656, 1369, 1169, 777 cm^{-1} .

(c) A mixture of the ester from (b) above (9.0 g, 36.4 mmole) and 2,6-diisopropylaniline (7.0 g) in 400 mL methylene chloride was cooled to 0 °C and 8.0 g dicyclohexylcarbodiimide was added all at once. The reaction mixture was stirred at 0 °C and was allowed to slowly warm to room temperature and was then stirred overnight at room temperature. The reaction mixture was refluxed gently for 2 hours and then concentrated to dryness. The residue was taken up in ethyl acetate, washed with 10% citric acid solution, NaHCO₃ (aq) and NaCl (aq). The organic layer was dried (MgSO₄), filtered, and concentrated to an off-white solid which was slurried in hexane and collected by filtration to give 3-[[2,6-bis(1-methylethyl)phenyl]amino]-2-[[[(1,1-dimethylethoxy)carbonyl]amino]-3-oxopropanoic acid, ethyl ester, 9.51 g (64%). IR (KBr) 3267, 2966, 1666, 1528, 1311, 735 cm^{-1} .

(d) The ester from (c) above (7.7 g, 19 mmole) was taken up in 50 mL methanol and 25 mL 1N NaOH was added at room temperature. The reaction mixture was concentrated on the rotary, water added, 5 mL more 1N NaOH added, and 10 mL methanol added. The mixture was heated briefly (~5 minutes) on the steam bath, then concentrated on the rotary evaporator to remove methanol, diluted with water and washed with ethyl acetate. The aqueous layer was made acidic with citric acid solution, saturated with NaCl(s), and extracted with ethyl acetate. The ethyl acetate solution was dried (MgSO₄), filtered, and concentrated to give 3-[[2,6-bis(1-methylethyl)phenyl]amino]-2-[[[(1,1-dimethylethoxy)carbonyl]amino]-3-oxopropanoic acid as a white solid, 5.69 g, 79.5%. IR (KBr) 3307, 2968, 1692, 1661, 1507, 1166, 744 cm^{-1} .

(e) Carbonyl diimidazole (2.5 g) was added to a mixture of 5.0 g (13.2 mmole) of the acid obtained in (d) above and 200 mL CH₂Cl₂ at room temperature. The resulting yellow solution was warmed to 30 °C for ~5 minutes and then 2.5 g N-benzyl isopropylamine was added. The reaction mixture was stirred overnight at room temperature, concentrated to dryness, and the residue taken up in ethyl acetate. The solution was washed with H₂O, 10% citric acid solution, NaHCO₃ (aq), and brine, dried (MgSO₄), filtered, and concentrated to a yellow oil. The oil was purified by filtration through silica gel (70-230 mesh) using 8/2 hexane/EtOAc as eluant. The title compound was obtained as an oil/foam, 4.96 g (73.7%). IR (KBr) 3278, 1729, 1669, 1499, 1364, 1282, 781 cm^{-1} .

EXAMPLE 10

237 dt

2-Amino-N'-[2,6-bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-(phenylmethyl) propanediamide

Trifluoroacetic acid (15 mL) was added to the product of Example 9 (2.47 g, 4.8 mmole) at room temperature. The reaction mixture was allowed to sit at room temperature over the weekend (2 days). The reaction mixture was concentrated to a viscous oil which was partitioned between NaHCO₃ (aq) and ethyl acetate. The ethyl acetate solution was washed with NaCl (aq), dried (MgSO₄), filtered, and concentrated to give the title compound as an off-white foam, 2.81 g (94.3%). IR (KBr) 3297, 2965, 1646, 1496, 925, 729 cm^{-1} .

EXAMPLE 11

N'-[2,6-Bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-(phenylmethyl)-2-[[[(propylamino)carbonyl]amino]-propanediamide

Propyl isocyanate (0.5 mL) was added to the product of Example 10 (0.36 g, 0.88 mmole) in 15 mL ethyl acetate at room temperature. The reaction mixture was concentrated on the rotary evaporator and the residue was treated a second time with .5 mL propyl isocyanate in ethyl acetate. The volatiles were removed in vacuo and the residue was allowed to sit overnight at room temperature. Addition of

hexane/EtOAc 1/1 caused precipitation of a white solid which was collected by filtration to give 0.32 g (75%) of the title compound. IR (KBr) 3362, 1631, 1466, 732 cm^{-1} .

EXAMPLE 12

N'-[2,6-Bis(1-methylethyl)phenyl]-2-[(4-fluorobenzoyl)amino]-N-(1-methylethyl)-N-(phenylmethyl)-propanediamide

237/22

10 A mixture of the product of Example 10 (0.33 g, 0.81 mmole) and excess triethylamine in ethyl acetate was treated with 0.17 g 4-F benzoyl chloride at room temperature. The reaction mixture was allowed to sit 5 days at room temperature. The reaction mixture was then diluted with ethyl acetate, washed with Na_2CO_3 - (aq), 1N HCl, NaCl (aq), dried (MgSO_4), filtered, and concentrated to give the title compound as a white solid, 0.38 g (88.4%). IR (KBr) 3272, 2967, 1625, 1489, 1237, 768 cm^{-1} .

15

EXAMPLE 13

20 N'-[2,6-Bis(1-methylethyl)phenyl]-2-[[[(2-methoxyphenyl)amino]carbonyl]amino]-N-(1-methylethyl)-N-(phenylmethyl) propanediamide

A solution of the product of Example 10 (0.35 g, 0.85 mmole) in 15 mL ethyl acetate was treated with 0.14 g 2-methoxyphenylisocyanate. The reaction mixture was concentrated to a viscous oil. The oil was dissolved in ethyl acetate and allowed to sit 5 days at room temperature. A white solid was formed and upon the addition of hexane was collected by filtration to give the title compound, 0.33 g (70%). IR (KBr) 3374, 1686, 1546, 1516, 1443, 743 cm^{-1} .

25

EXAMPLE 14

30 N'-[2,6-Bis(1-methylethyl)phenyl]-2-[[[4-(dimethylamino)phenyl]amino]thioxomethyl]amino]-N-(1-methylethyl)-N-(phenylmethyl)propanediamide

35 A mixture of the product of Example 10 (0.32 g, 0.78 mmole) and 0.16 g 4-dimethylaminophenyl isothiocyanate were allowed to sit 8 days at room temperature in ethyl acetate. The reaction mixture was concentrated to a viscous oil, which crystallized upon the addition of 9/1 hexane/ethyl acetate. The product was collected by filtration to give the title compound, 0.40 g (87%). IR (KBr) 3316, 3199, 1515, 1362, 1173, 732 cm^{-1} .

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CHART I

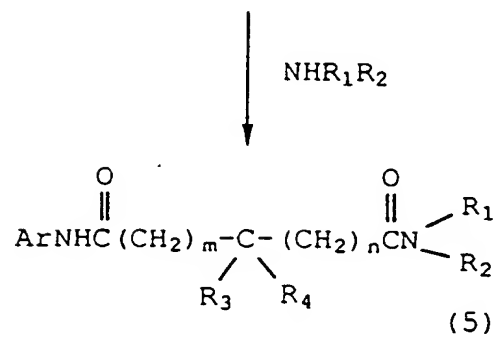
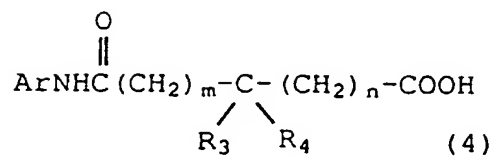
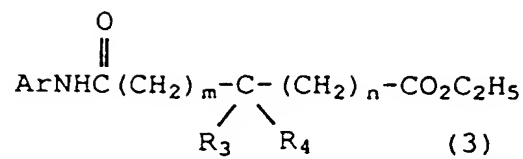
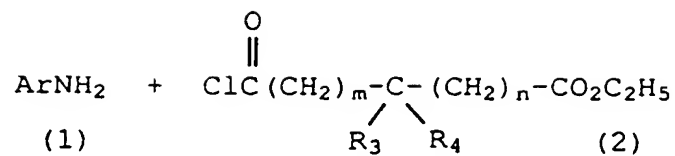
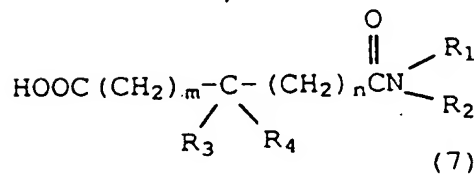
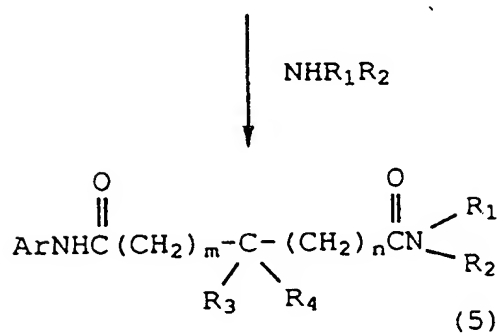
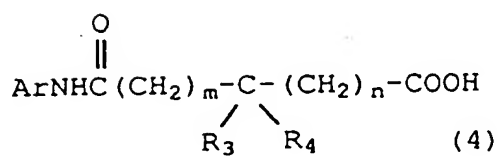
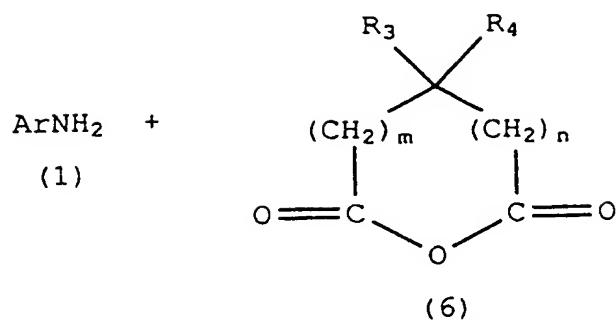
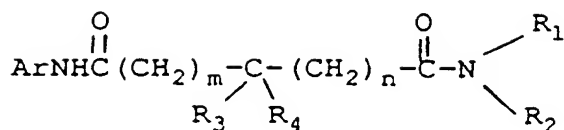


CHART II



Claims

1. A compound of the following general Formula I



I

wherein Ar is

(a) phenyl(CH₂)_x wherein X is zero to 2 and wherein the phenyl ring is unsubstituted or is substituted with

from 1 to 3 substituents selected from
alkyl having from 1 to 6 carbon atoms and which is straight or branched,
alkoxy having from 1 to 6 carbon atoms and which is straight or branched,

phenoxy,

hydroxy,

fluorine,

chlorine,

bromine,

nitro,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms,

-NR₅R₆ wherein

R₅ and R₆ are independently hydrogen or alkyl of from 1 to 4 carbon atoms;

(b) 1- or 2-naphthyl which is unsubstituted or substituted with

alkyl having from 1 to 6 carbon atoms and which is straight or branched;

alkoxy having from 1 to 6 carbon atoms and which is straight or branched,

hydroxy,

fluorine,

chlorine,

bromine,

nitro,

trifluoromethyl,

-COOH,

-COOalkyl wherein alkyl has from 1 to 4 carbon atoms,

-NR₅R₆ wherein R₅ and R₆ have the meanings defined above;

wherein each of m and n is independently zero, one, or two;

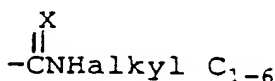
wherein each of R₃ and R₄ is independently (a) hydrogen;

(b) a straight or branched alkyl group having from 1 to 10 carbon atoms;

(c) a straight chain alkyl group having from 1 to 10 carbon atoms wherein the terminal carbon atom is substituted with hydroxy or NR₅R₆ wherein R₅ and R₆ have the meanings defined above;

(d) R₃ is hydrogen and R₄ is the group -NHR₁₀ wherein R₁₀ is -C(=O)alkyl C₁₋₆ wherein the alkyl moiety is straight or branched; -(C=O)O-t-C₄H₉;

-C(=O)OCH₂C₆H₅;



wherein X is oxygen or sulfur and the alkyl moiety is straight or branched;



wherein X is oxygen or sulfur and Ph is phenyl or substituted phenyl wherein the substituents vary in number from 1 to 3 and are selected from chlorine, fluorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched or NR₅R₆ wherein R₅ and R₆ have the meanings defined

hereinabove; or



5

wherein Ph is phenyl or phenyl substituted with from 1 to 3 substituents selected from chlorine, fluorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR_5R_6 wherein R_5 and R_6 have the meanings defined hereinabove; or

10

(e) R_3 is hydrogen and R_4 is $\text{NR}_{12}\text{R}_{13}$ wherein each of R_{12} and R_{13} is selected from hydrogen, straight or branched alkyl having from 1 to 6 carbon atoms, phenyl or benzyl or phenyl or benzyl substituted on any positions 2 through 6 of the aromatic ring with from 1 to 3 substituents selected from fluorine, chlorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR_5R_6 wherein R_5 and R_6 have the meanings defined hereinabove;

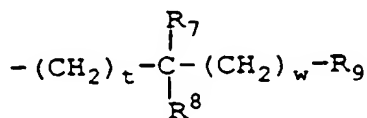
15

wherein each of R_1 and R_2 is independently

(a) hydrogen,

(b) the group

20



25

wherein t is zero to 4; w is zero to 4 with the proviso that the sum of t and w is not greater than 5; R_7 and R_8 are independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when R_7 is hydrogen, R_8 can be selected from the group defined for R_3 ; and R_9 is phenyl or phenyl substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 6 carbon atoms, straight or branched alkoxy having from 1 to 6 carbon atoms, the group

30

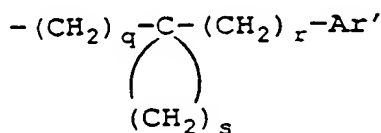


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alkyl wherein e is zero, one or two, and alkyl is straight or branched and has from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, $-\text{COOH}$, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or $-\text{NR}_5\text{R}_6$ wherein R_5 and R_6 have the meanings defined above;

40

(c) the group



45

wherein q is zero to 3; r is zero to 2; s is 2 to 6; and Ar' is phenyl,

50

1- or 2-naphthyl,

phenyl or 1- or 2-naphthyl substituted with alkyl of from one to six carbon atoms,

alkoxy of from one to six carbon atoms,

hydroxy,

benzyloxy,

55

fluorine,

chlorine,

bromine,

nitro.

trifluoromethyl,

-NH-COCH₃,

-CONH₂,

-COOH,

5 -COOalkyl wherein alkyl has from one to four carbon atoms,

-CH₂COOH,

-CH₂CONH₂,

-NR₅R₆ wherein R₅ and R₆ have the meanings defined above;

10 (d) a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and which is saturated or contains from 1 to 3 double bonds;

(e) an alkyl group having from 1 to 6 carbon atoms wherein the terminal carbon is substituted with hydroxy,

-NR₅R₆ where in R₅ and R₆ have the meanings defined above, or -COOalkyl wherein alkyl is straight or branched and has from 1 to 4 carbon atoms;

15 (f) -(CH₂)_pQ wherein p is a number from zero to 3 and Q is a 5- or 6-membered monocyclic or fused bicyclic heterocycle containing at least 1 to 4 nitrogen, oxygen, or sulfur atoms in at least one ring member;

(g) phenyl or phenyl substituted with from 1 to 3 substituents selected from straight or branched alkyl having from 1 to 6 carbon atoms, alkoxy which is straight or branched and has from 1 to 6 carbon atoms, alkylthio which is straight or branched and has from 1 to 6 carbon atoms, -NR₅R₆ wherein R₅ and R₆ have the meanings defined above, hydroxy, nitro, chlorine, fluorine, bromine, or trifluoromethyl;

20 (h) NR₁R₂ taken together are phenothiazine or form a monocyclic heterocyclic group selected from pyrrolidino, piperidino, morpholino, or piperazino, each of which is unsubstituted or is substituted with one substituent selected from benzhydryl, straight or branched alkyl having from 1 to 6 carbon atoms, ω-hydroxyalkyl having from 1 to 6 carbon atoms, phenyl, benzyl, or substituted phenyl or substituted benzyl wherein the substituents vary from 1 to 3 and can be on any position of 2 through 6 of the aromatic ring
25 and are selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein Ar is phenyl(CH₂)_x wherein x is zero or two.

3. A compound of Claim 2 wherein the phenyl ring is unsubstituted.

30 4. A compound of Claim 2 wherein the phenyl ring is substituted.

5. A compound of Claim 4 wherein the phenyl ring is substituted on the 2,6-positions.

6. A compound of Claim 1 wherein each of R₁ and R₂ is independently hydrogen or the group:



40 7. A compound of Claim 1 wherein each of R₁ and R₂ is independently hydrogen or the group:



8. A compound of Claim 1 which is

50 N-[2,6-bis(1-methylethyl)phenyl]-N'-(2,2-diphenylethyl)propanediamide,

N-[2,6-bis(1-methylethyl)phenyl]-N'-(1-phenylcyclopentyl)methylpropanediamide,

N'-[2,6-bis(1-methylethyl)phenyl]-N-(diphenylmethyl)propanediamide,

N'-[2,6-bis(1-methylethyl)phenyl]-N,N-bis-(phenylmethyl)propanediamide,

N'-[2,6-bis(1-methylethyl)phenyl]-N-(diphenylmethyl)-N-(1-methylethyl)propanediamide,

55 N-[2,6-bis(1-methylethyl)phenyl]-β-oxo-4-phenyl-1-piperazinepropanamide,

N-[2,6-bis(1-methylethyl)phenyl]-β-oxo-4-phenyl-1-piperidinepropanamide,

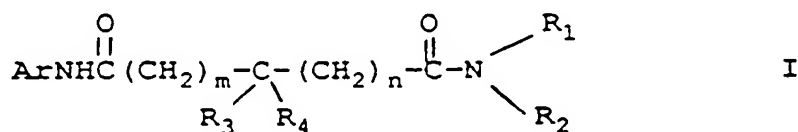
(S)-N-[2,6-bis(1-methylethyl)phenyl]-2-(hydroxymethyl)-β-oxo-1-pyrrolidinepropanamide,

N'-[2,6-bis(1-methylethyl)phenyl]-N-methyl-N-[2-(2-pyridyl)ethyl]propanediamide,

- N'-[2,6-bis(1-methylethyl)phenyl]-N(1-methylethyl)-N-(phenylmethyl) propanediamide,
 N,N-dipentyl-N'-[2,6-bis(1-methylethyl)phenyl]propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(phenylmethyl) propanediamide,
 N,N-di-(2-hydroxyethyl)-N'-[2,6-bis(1-methylethyl)phenyl]propanediamide,
 5 N'-[2,6-bis(1-methylethyl)phenyl]-N-[(4-fluorophenyl)methyl]-N-(1-methylethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-dimethylaminoethyl)-N'-(phenylmethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-hydroxyethyl)-N'-(phenylmethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(ethyl)-N'-(2-diethylaminoethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]- β -oxo-4-(2-hydroxyethyl)-1-piperazinepropanamide,
 10 N-[2,6-bis(1-methylethyl)phenyl]- β -oxo-1-morpholinepropanamide,
 N-[2,6-bis(1-methylethyl)phenyl]- β -oxo-1-thiomorpholinepropanamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-[2-cyanoethyl]-N'-(phenylmethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(diphenylmethyl)pentanamide,
 N'-[2,6-bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-[[4-(methylsulfinyl)phenyl]methyl]propanediamide;
 15 N'-[2,6-bis(1-methylethyl)phenyl]-2,2-dimethyl-N-(1-methylethyl)-N-(phenylmethyl)propanediamide,
 N'-[2,6-bis(1-methylethyl)phenyl]-N(1-methylethyl)-N-phenylpropanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-[(3-pyridinyl)methyl]propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]- β -oxo-4-(phenylmethyl)-1-piperazinepropanamide,
 N'-[2,6-bis(1-methylethyl)phenyl]-N-(1-methylethyl)-N-[[4-(methylthio)phenyl]methyl] propanediamide,
 20 N-[3-[[2,6-bis(1-methylethyl)phenyl]amino]-1,3-dioxopropyl]-N-phenylglycine, ethyl, ester;
 N-[2,6-bis(1,1-dimethylethyl)phenyl]-4-(2-methoxyphenyl)- β -oxo-1-piperazinepropanamide,
 N-[2,6-bis(1-methylethyl)phenyl]-1-(diphenylmethyl)-1-piperazinepropanamide,
 N-[2,6-bis(1-methylethyl)phenyl]- β -[[4-(4-methoxyphenyl)methyl] (2-pyridinyl)amino]- β -oxopropanamide,
 N-[2,6-bis(1-methylethyl)phenyl]- β -oxo-10H-phenothiazine-10-propanamide,
 25 N'-[2,6-bis(1-methylethyl)phenyl]-N-[(4-methoxyphenyl)methyl]-N-(2-pyrimidinyl)-propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-heptylpropanediamide,
 N,N'-bis[2,6-bis(1-methylethyl)phenyl]propanediamide,
 N'-[2,6-bis(1-methylethyl)phenyl]-N-[[4-(dimethylamino)phenyl]methyl]-N-(1-methylethyl)propanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(1,1,3,3-tetramethylbutyl) propanediamide,
 30 N'-[2,6-bis(1-methylethyl)phenyl]-N-methyl-N-octylpropanediamide,
 N-[2,6-bis(1-methylethyl)phenyl]-N'-(1,1-dimethyl-2-phenylethyl) propanediamide,
 N-[2,6-bis(dimethylamino)phenyl]-2,6-bis(1-methylethyl)phenyl]propanediamide, and N'-[2,6-bis(1-
 methylethyl)phenyl]-N-methyl-N-octadecylpropanediamide
 9. A process for preparing a compound of formula I

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wherein Ar is

- (a) phenyl(CH₂)_x- wherein X is zero to 2 and wherein the phenyl ring is unsubstituted or is substituted with
 45 from 1 to 3 substituents selected from
 alkyl having from 1 to 6 carbon atoms and which is straight or branched,
 alkoxy having from 1 to 6 carbon atoms and which is straight or branched,
 phenoxy,
 hydroxy,
 50 fluorine,
 chlorine,
 bromine,
 nitro,
 trifluoromethyl,
 55 -COOH,
 -COOalkyl wherein alkyl has from 1 to 4 carbon atoms,
 -NR₅R₆ wherein
 R₅ and R₆ are independently hydrogen or alkyl of from 1 to 4 carbon atoms;

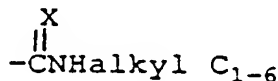
(b) 1- or 2-naphthyl which is unsubstituted or substituted with alkyl having from 1 to 6 carbon atoms and which is straight or branched; alkoxy having from 1 to 6 carbon atoms and which is straight or branched, hydroxy,

5 fluorine,
chlorine,
bromine,
nitro,
trifluoromethyl,

10 -COOH,
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms,
-NR₅R₆ wherein R₅ and R₆ have the meanings defined above;
wherein each of m and n is independently zero, one, or two;
wherein each of R₃ and R₄ is independently (a) hydrogen;

15 (b) a straight or branched alkyl group having from 1 to 10 carbon atoms;
(c) a straight chain alkyl group having from 1 to 10 carbon atoms wherein the terminal carbon atom is substituted with hydroxy or NR₅R₆ wherein R₅ and R₆ have the meanings defined above;
(d) R₃ is hydrogen and R₄ is the group -NHR₁₀ wherein R₁₀ is -C(=O)alkyl C₁₋₆ wherein the alkyl moiety is straight or branched; -C(=O)O-t-C₄H₉; -C(=O)OCH₂C₆H₅;

20



25 wherein X is oxygen or sulfur and the alkyl moiety is straight or branched;



30 wherein X is oxygen or sulfur and Ph is phenyl or substituted phenyl wherein the substituents vary in number from 1 to 3 and are selected from chlorine, fluorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched or NR₅R₆ wherein R₅ and R₆ have the meanings defined hereinabove; or

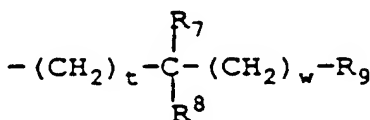
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40 wherein Ph is phenyl or phenyl substituted with from 1 to 3 substituents selected from chlorine, fluorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon atoms and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR₅R₆ wherein R₅ and R₆ have the meanings defined hereinabove; or

(e) R₃ is hydrogen and R₄ is NR₁₂R₁₃ wherein each of R₁₂ and R₁₃ is selected from hydrogen, straight or branched alkyl having from 1 to 6 carbon atoms, phenyl or benzyl or phenyl or benzyl substituted on any positions 2 through 6 of the aromatic ring with from 1 to 3 substituents selected from fluorine, chlorine, bromine, iodine, trifluoromethyl, lower alkyl having from 1 to 4 carbon and being straight or branched, lower alkoxy having from 1 to 4 carbon atoms and being straight or branched, or NR₅R₆ wherein R₅ and R₆ have the meanings defined hereinabove; wherein each of R₁ and R₂ is independently

50 (a) hydrogen,
(b) the group



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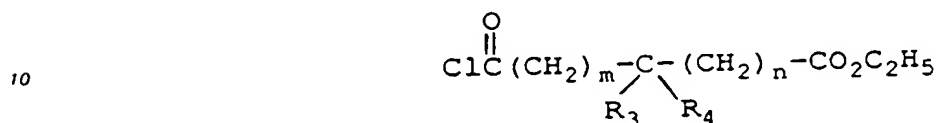
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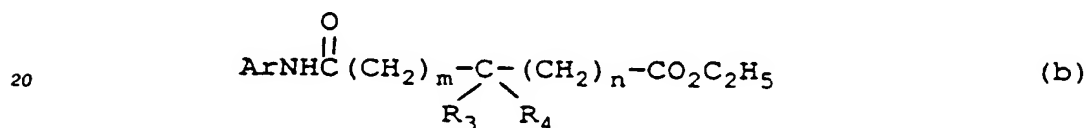
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and are selected from straight or branched alkyl having from 1 to 4 carbon atoms, straight or branched alkoxy having from 1 to 4 carbon atoms, hydroxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro; or of a pharmaceutically acceptable salt thereof, which comprises reacting an arylamine of the formula ArNH_2

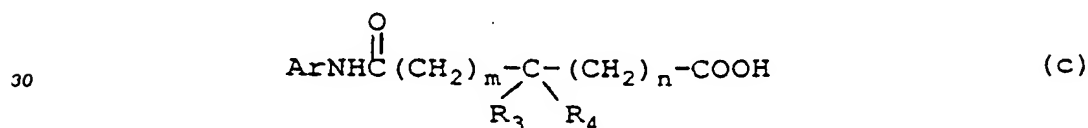
5 wherein Ar has the above meaning with an acid chloride of the formula



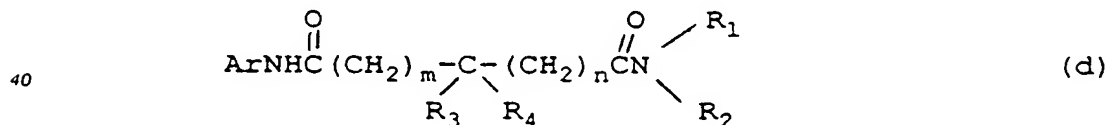
15 wherein m, n, R_3 and R_4 have the above meaning in an aprotic nonpolar solvent in the presence of a tertiary amine to give an ester amide of the formula



25 wherein n, m, Ar, R_3 and R_4 have the above meaning which is treated with a mild aqueous base to give an acid amide of the formula



35 wherein n, m, Ar and R_3 and R_4 have the above meaning which is converted to the bis amides of formula (d) by reaction with an amine of the formula HNR_1R_2

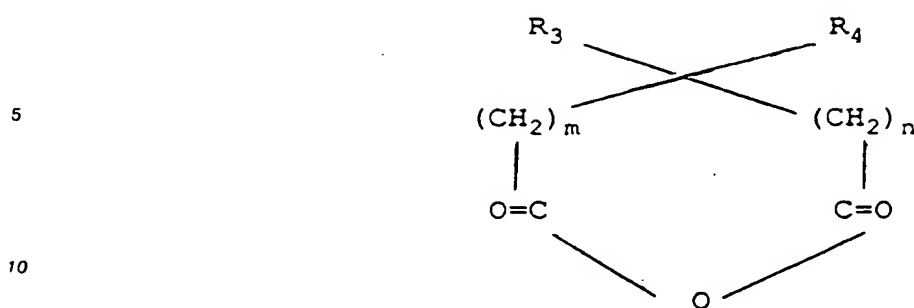


45 wherein Ar, R_1 , R_2 , R_3 , R_4 , m, and n have the above meaning except that R_4 is other than NHR_{10} or $\text{NR}_{12}\text{R}_{13}$,

or alternatively reacting an arylamine of the formula ArNH_2 wherein Ar has the above meaning with an acid anhydride of the formula

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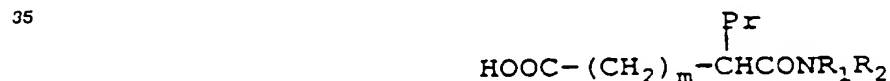
wherein R_3 , R_4 , m and n have the above meaning in an aprotic nonpolar solvent to give an amide acid of the formula (c) above which is converted to the bis-amide of formula (d) as defined above, and when a compound wherein R_4 is NHR_{10} or $\text{NR}_{12}\text{R}_{13}$, wherein R_{10} , R_{12} and R_{13} have the above meaning, is desired, reacting a compound of the formula



wherein m has the above meaning, R_{11} is lower alkyl and Pr is tert-butoxycarbonyl or benzyloxycarbonyl with a carbodiimide followed by the addition of an amine of the formula HNR_1R_2 wherein R_1 and R_2 are as defined above to give an ester amide of the formula

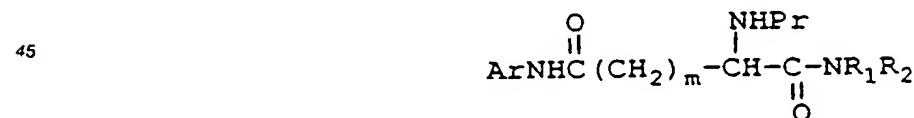


wherein R_1 , R_2 , R_{11} , Pr and m have the above meaning which is hydrolyzed to the corresponding amide acid of the formula



wherein m , R_1 , R_2 and Pr have the above meaning, which is treated with a carbodiimide and reacted with an amine of the formula ArNH_2

wherein Ar has the above meaning to give compounds of the formula



wherein R_1 , R_2 , Pr , m and Ar are as defined above which can be deprotected and acylated or alkylated, to give compounds of Claim 1 wherein R_4 is NHR_{10} or $\text{NR}_{12}\text{R}_{13}$, further, when R_3 and R_4 are hydrogen a compound of formula I if desired is treated with a mild base and then alkylated with a compound of the formulae

Hal-R_3 and/or Hal-R_4

wherein Hal is a halogen atom and R_3 and R_4 as defined above,

and if desired a pharmaceutically acceptable salt is formed with an organic or inorganic acid.

10. A process of Claim 9 for preparing a compound as defined in any of Claims 2 to 8.

11. A pharmaceutical composition containing a compound as defined in any of Claims 1 to 8 or as prepared

by the process of Claims 9 or 10 together with a pharmaceutically acceptable carrier.

12. Use of a compound as defined in any of Claims 1 to 8 or as prepared by the process of Claims 9 or 10 for the preparation of a pharmaceutical composition useful for treating hypercholesterolemia and atherosclerosis.

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FIG. 1

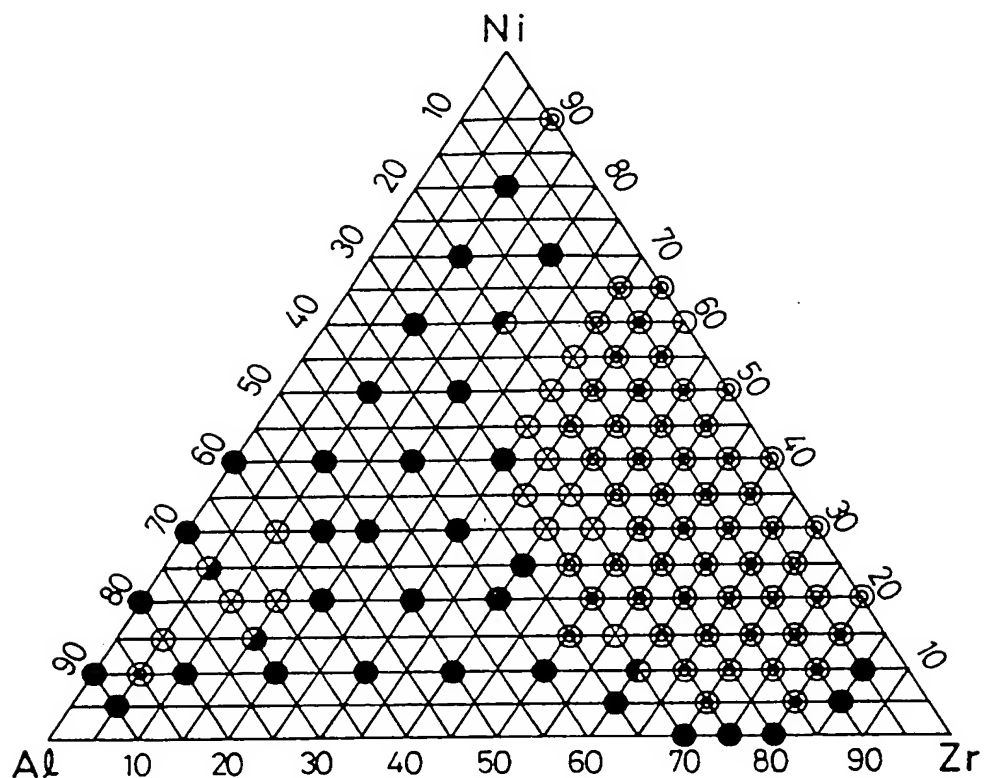
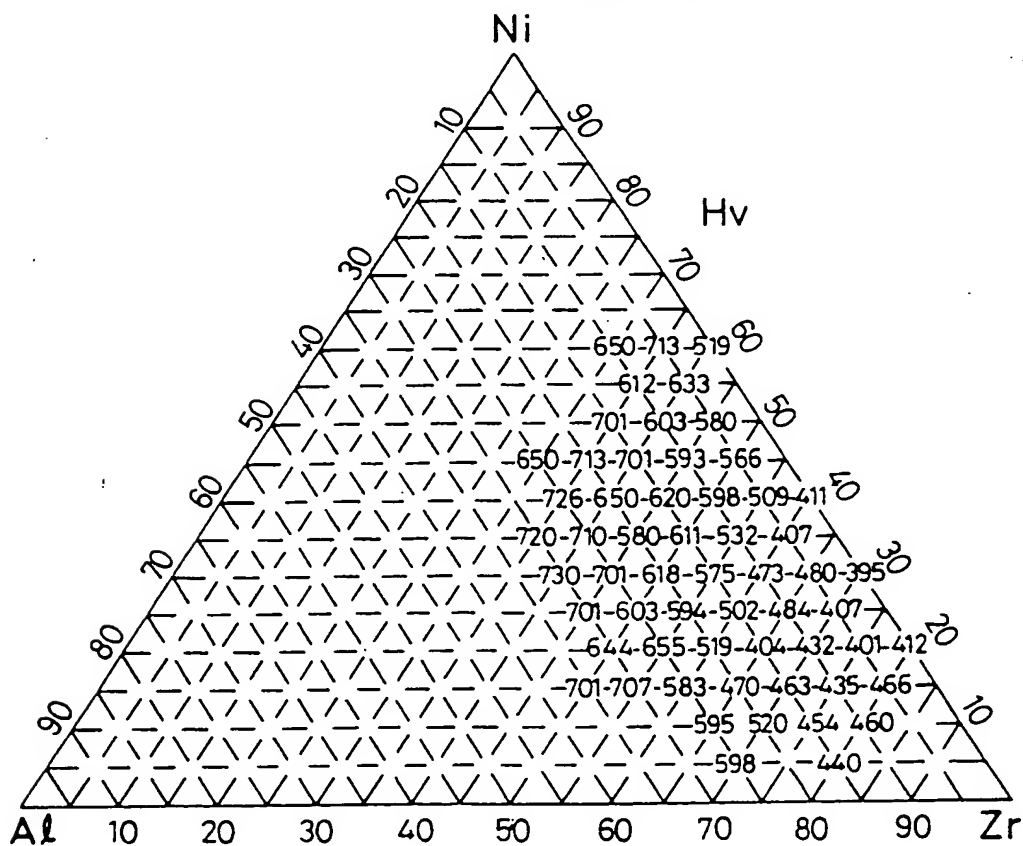


FIG. 2



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FIG. 3

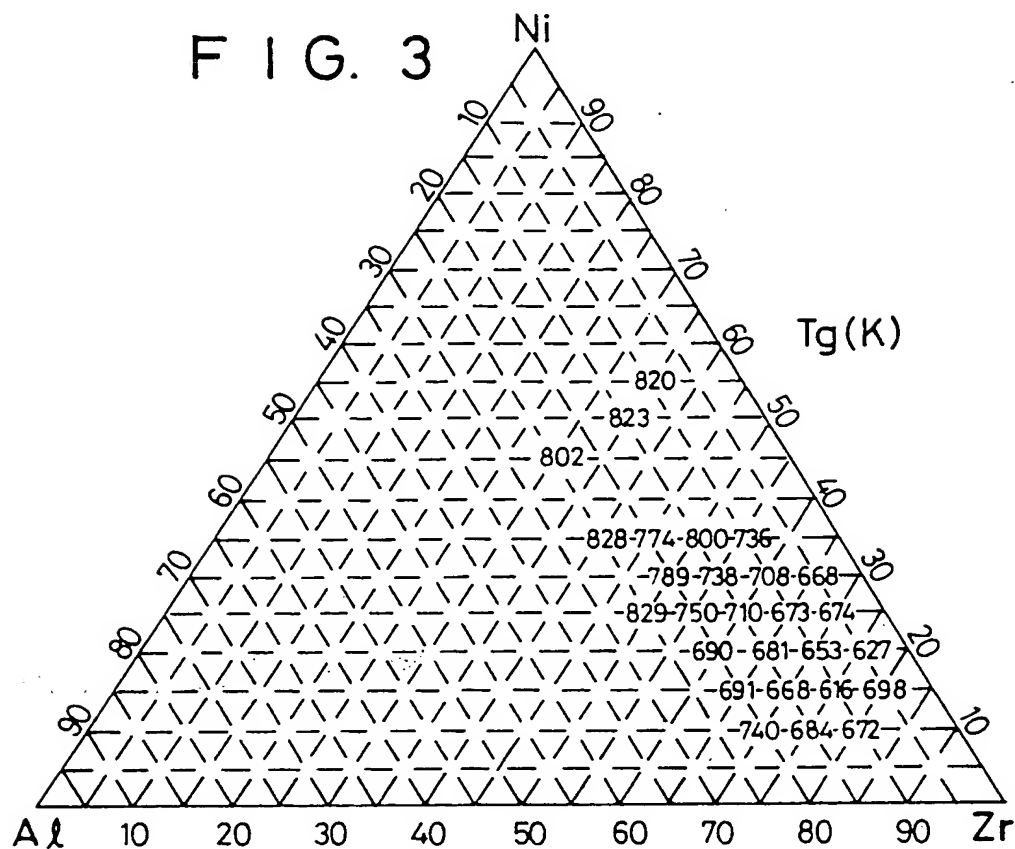
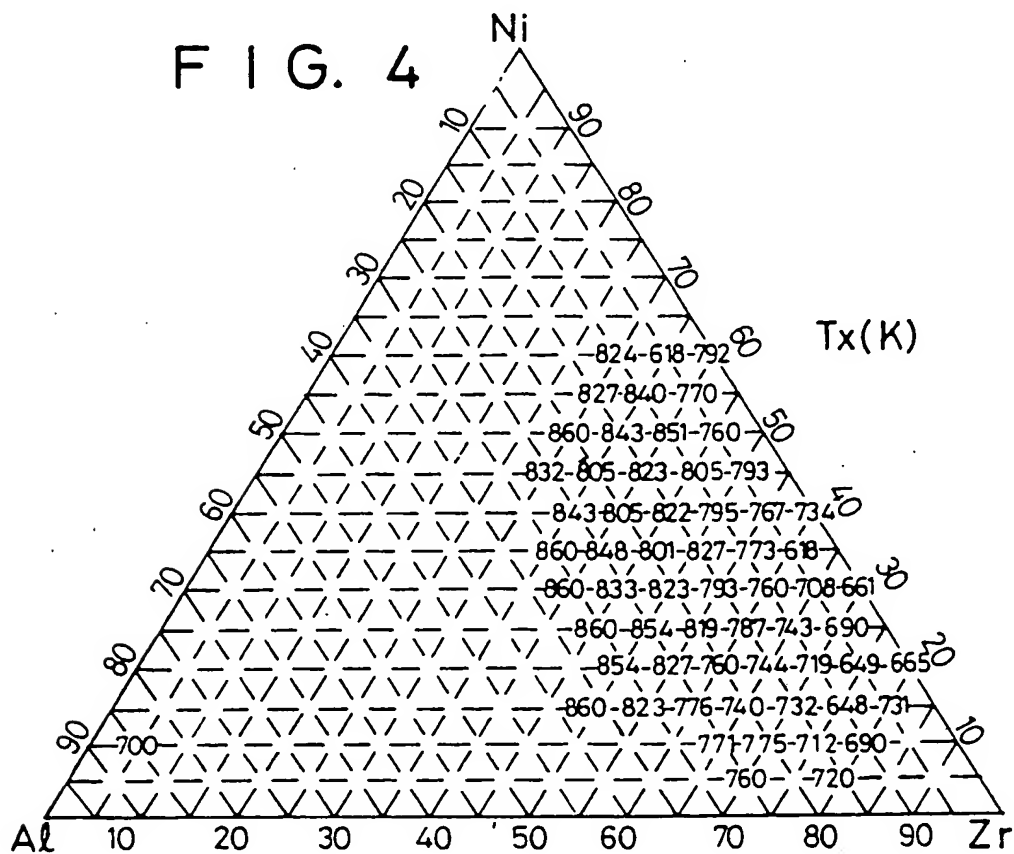


FIG. 4



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FIG. 5

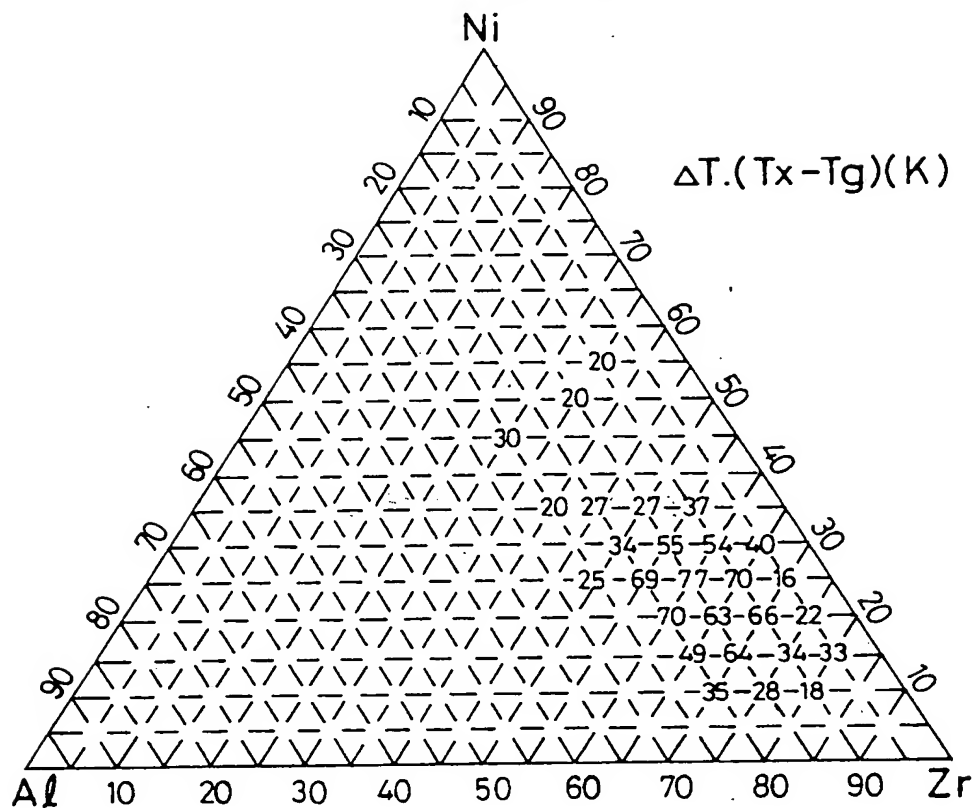
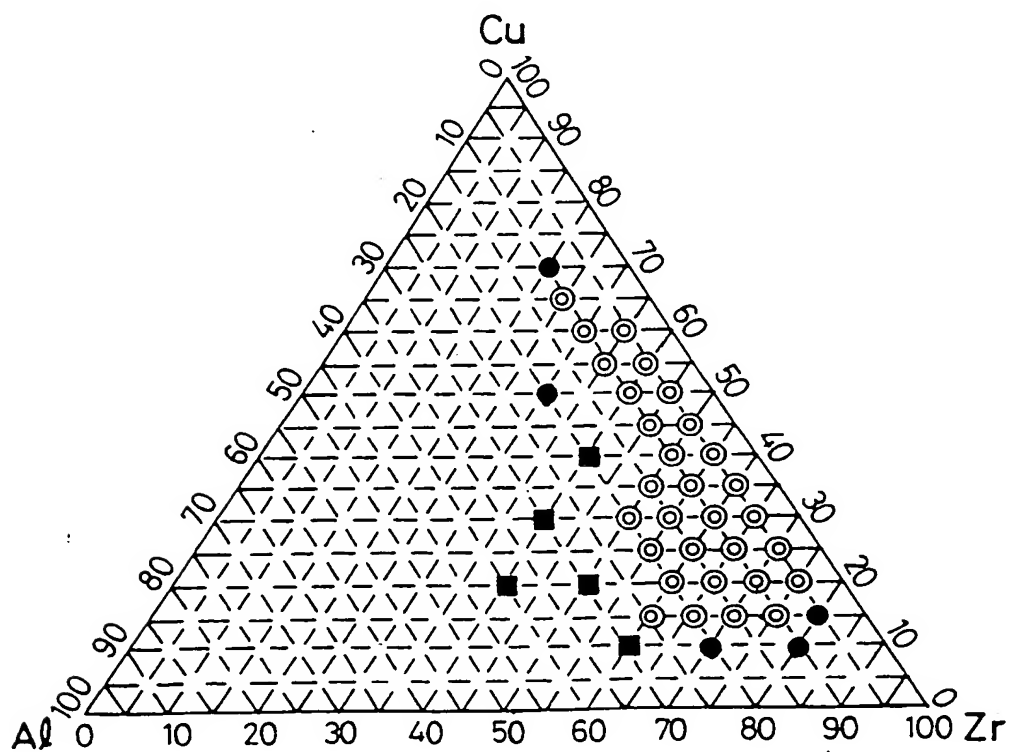


FIG. 6



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FIG. 7

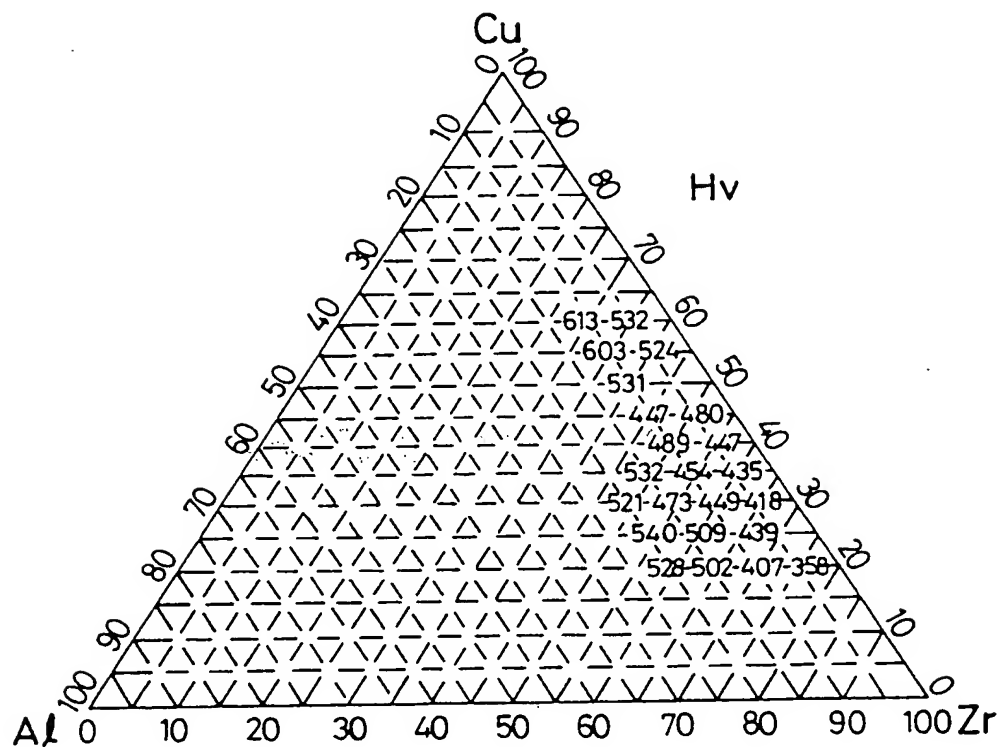
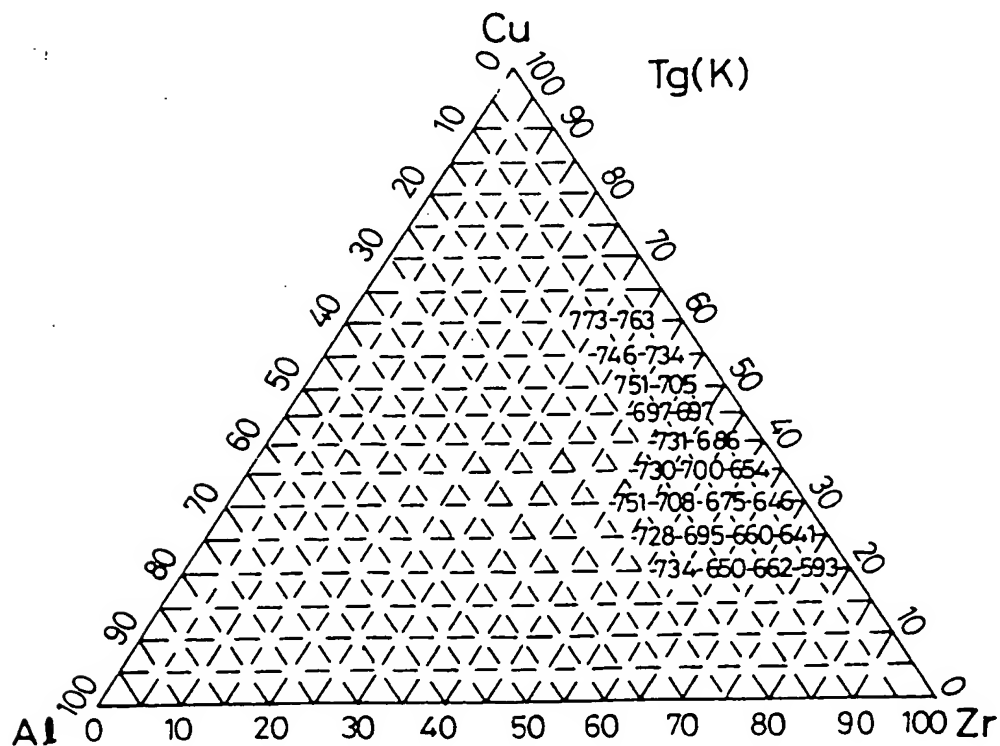


FIG. 8



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FIG. 9

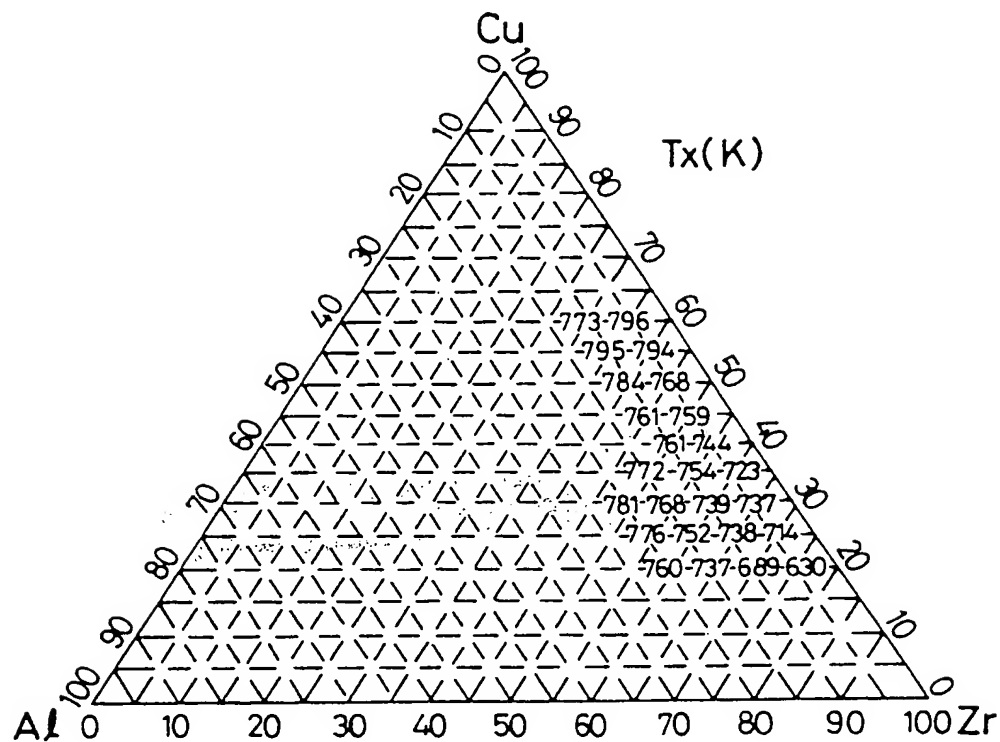
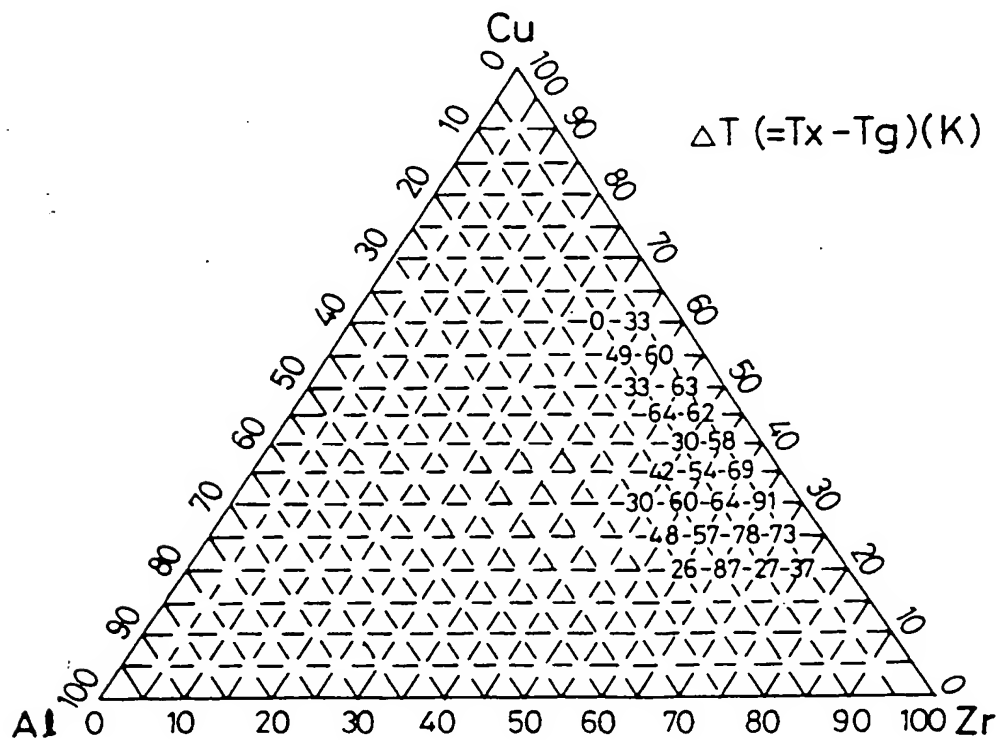


FIG. 10



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FIG. 11

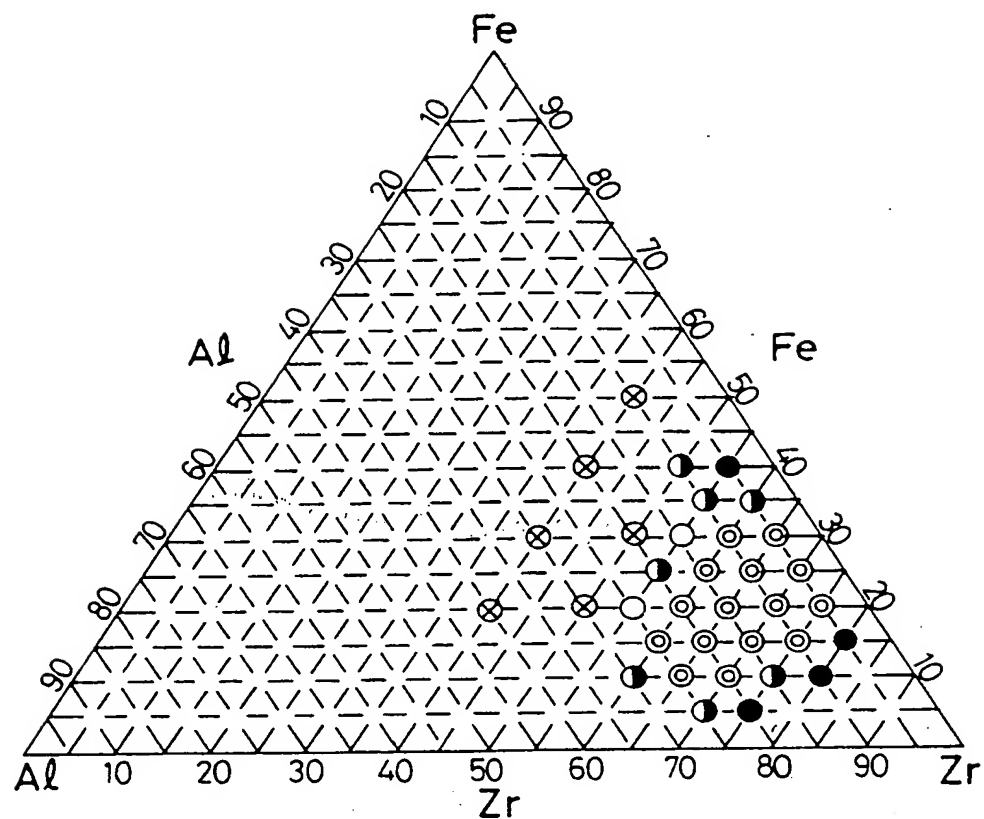
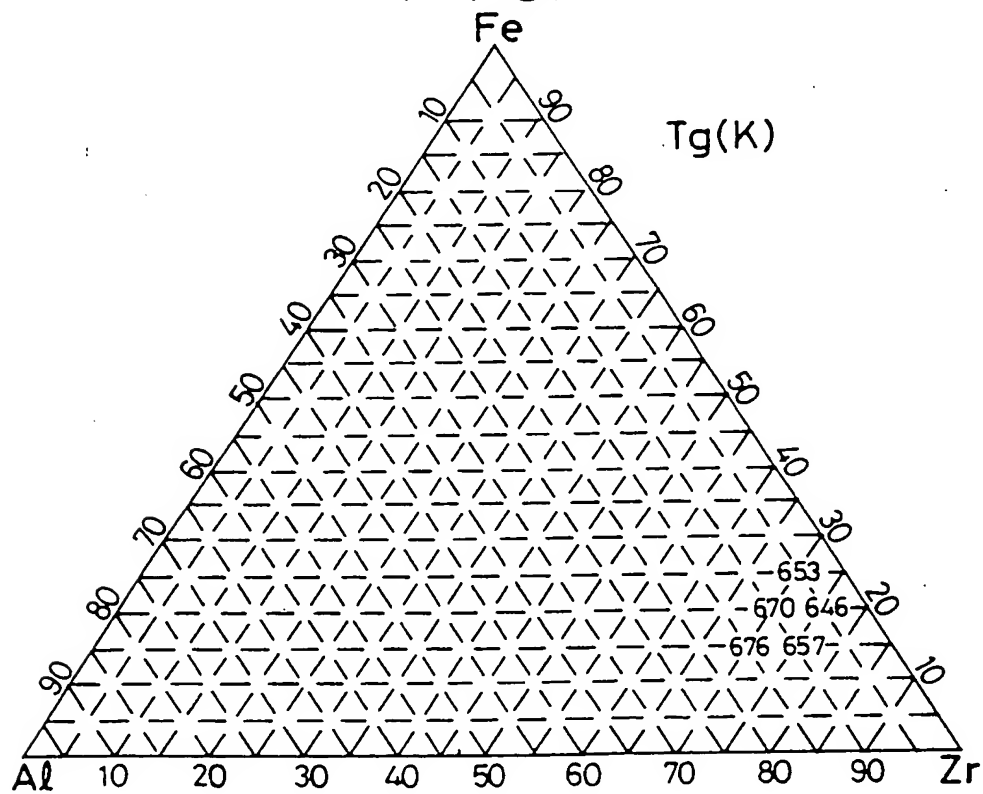


FIG. 12



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FIG. 13

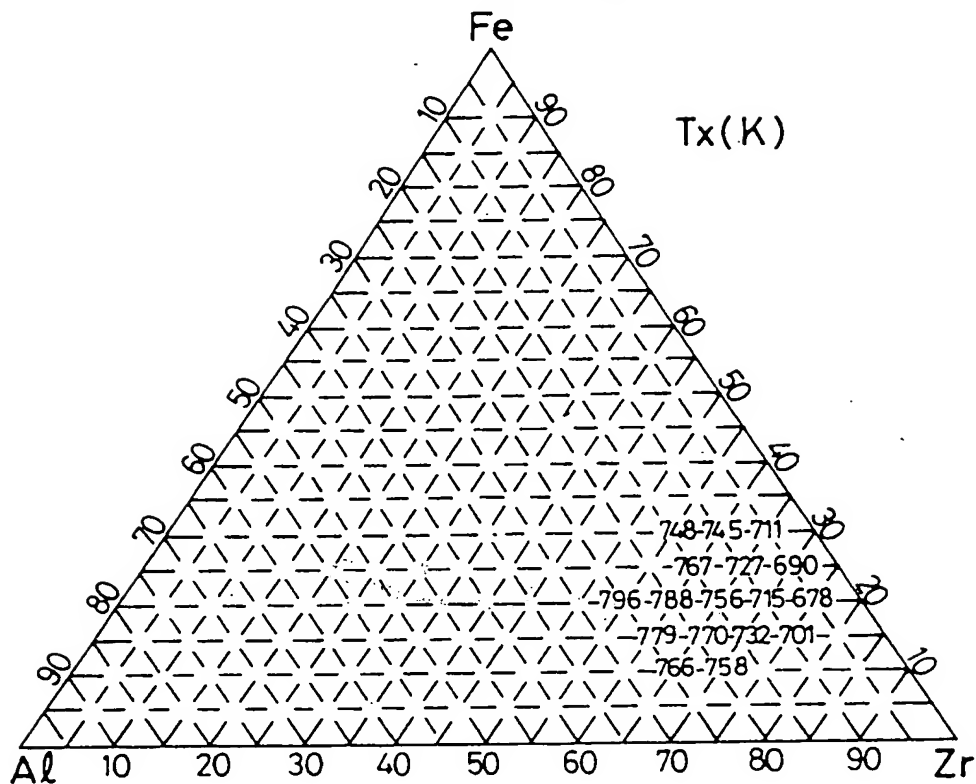
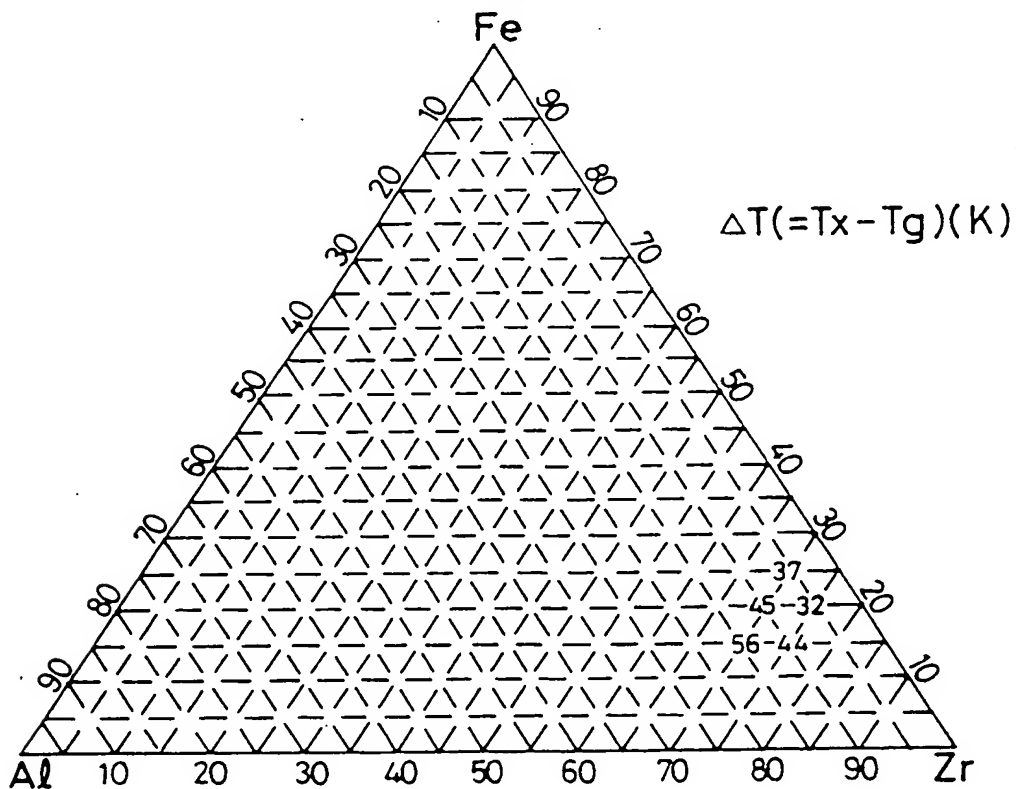


FIG. 14



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FIG. 15

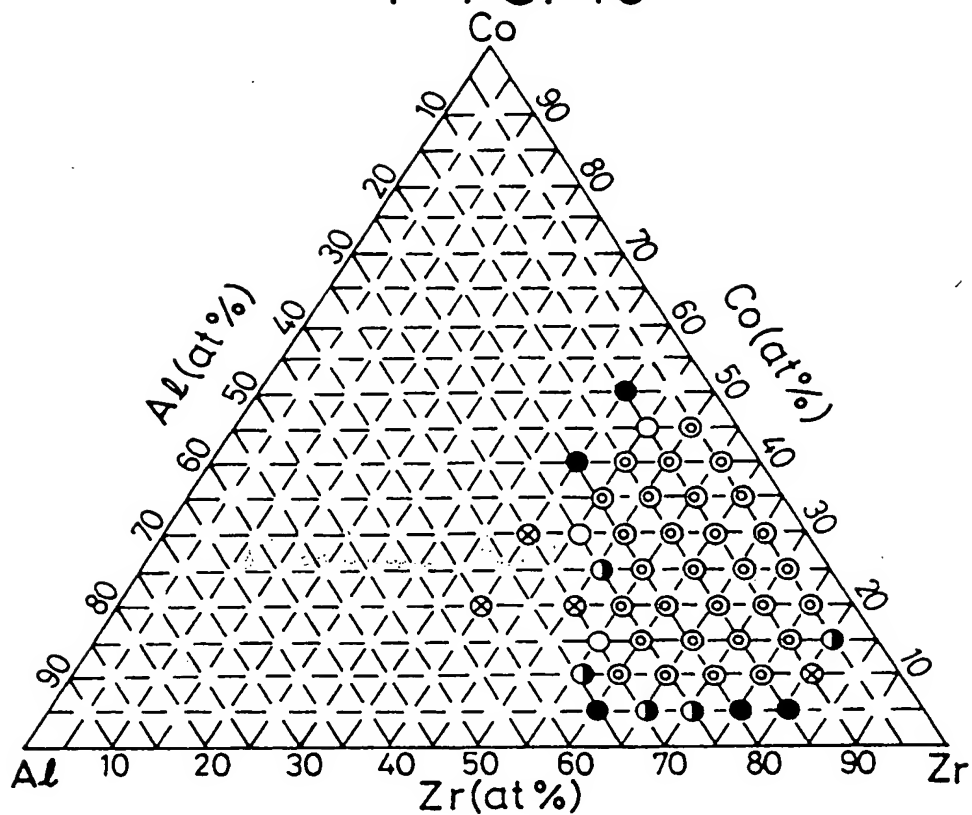
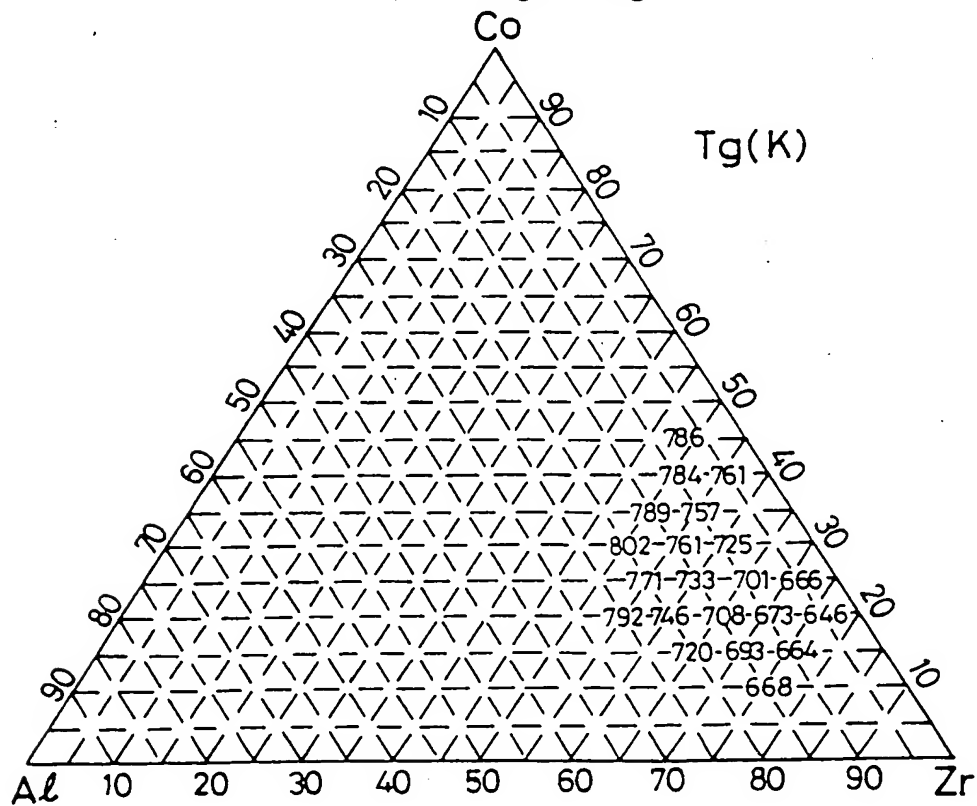


FIG. 16



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FIG. 17

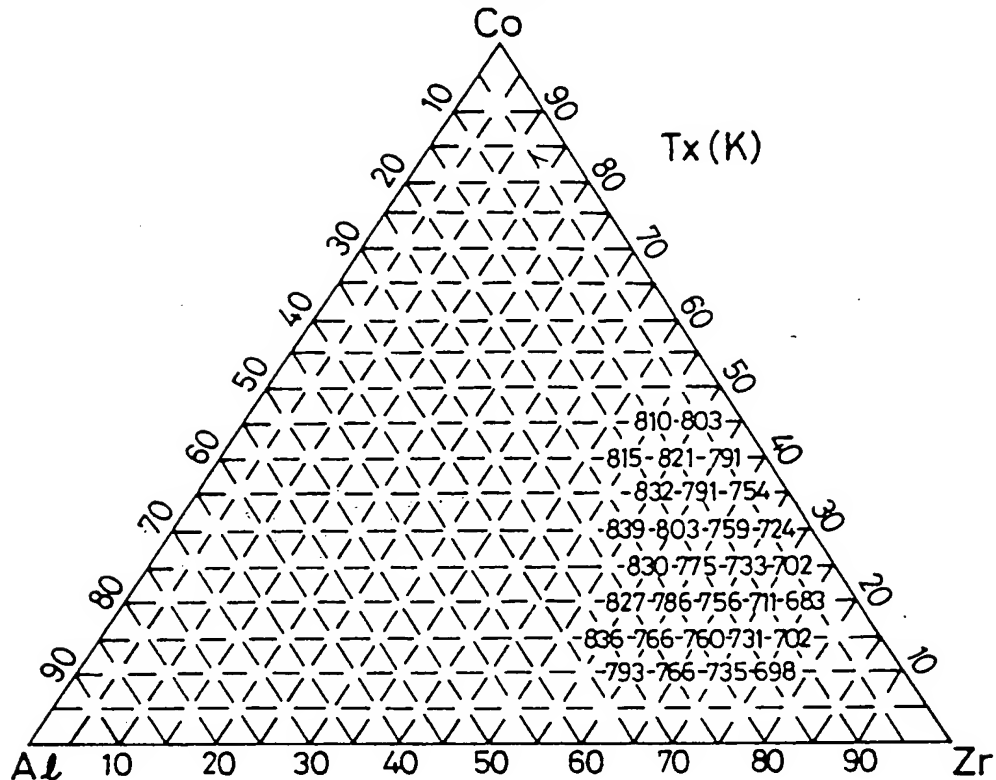
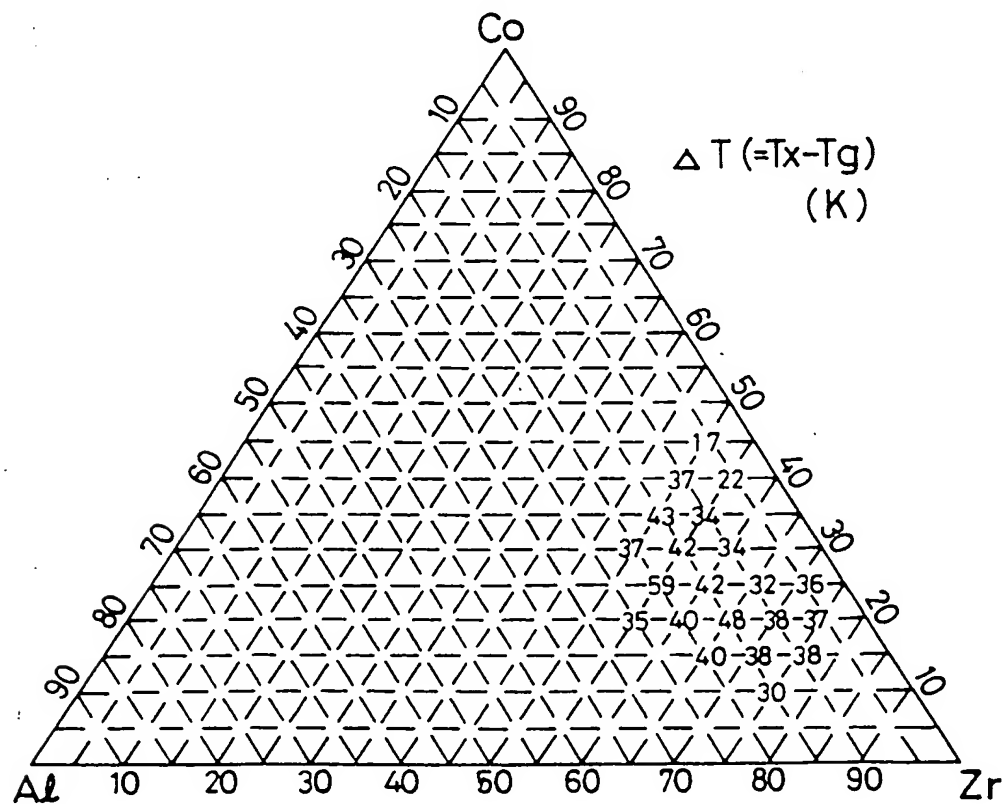


FIG. 18



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FIG. 19

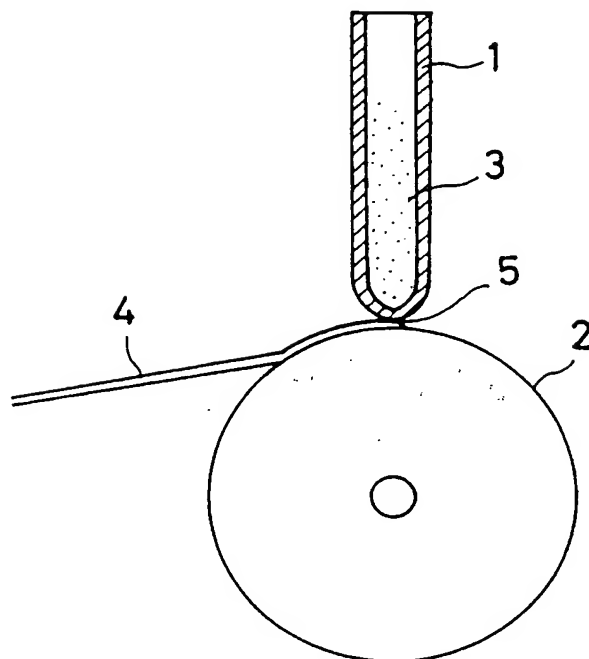
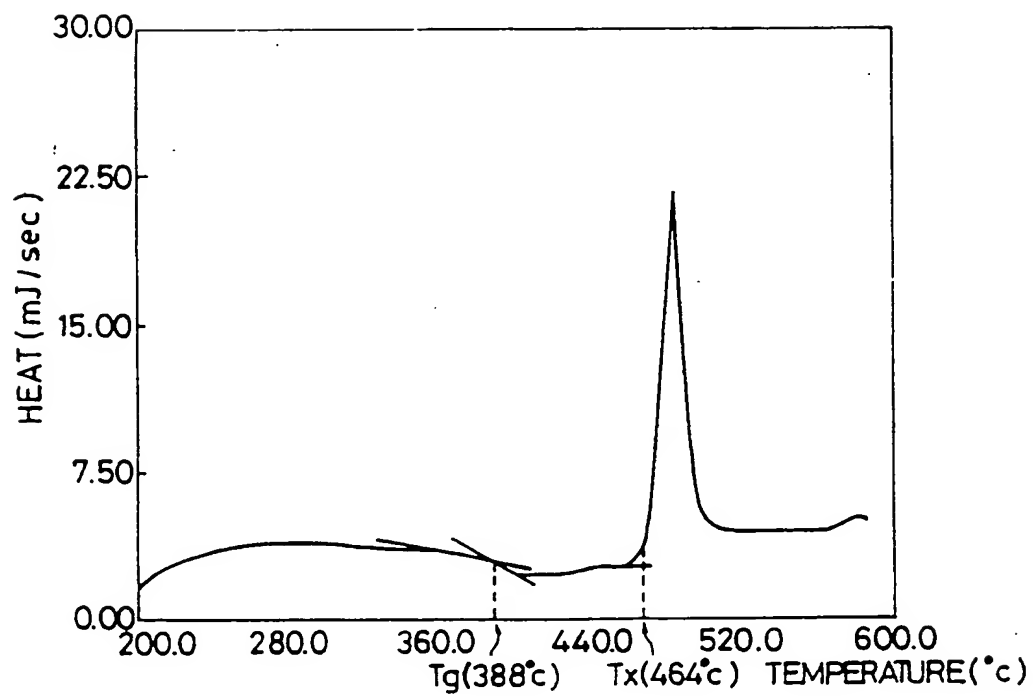


FIG. 20



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FIG. 21

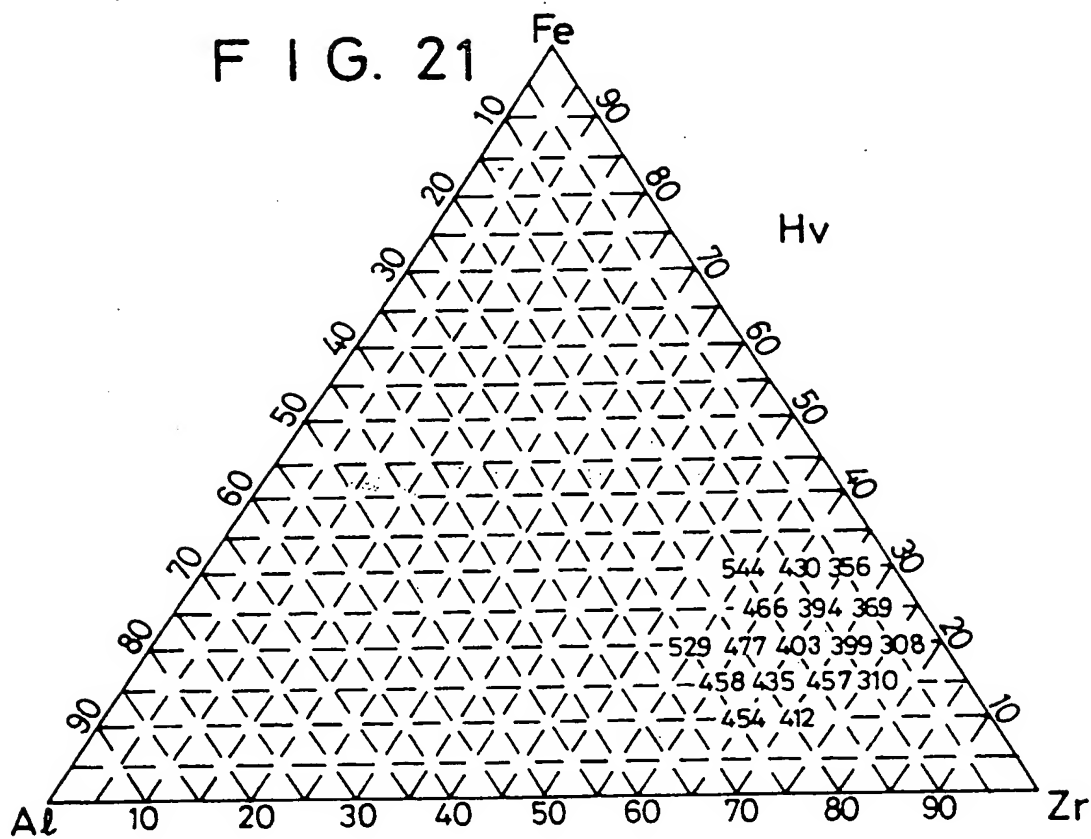
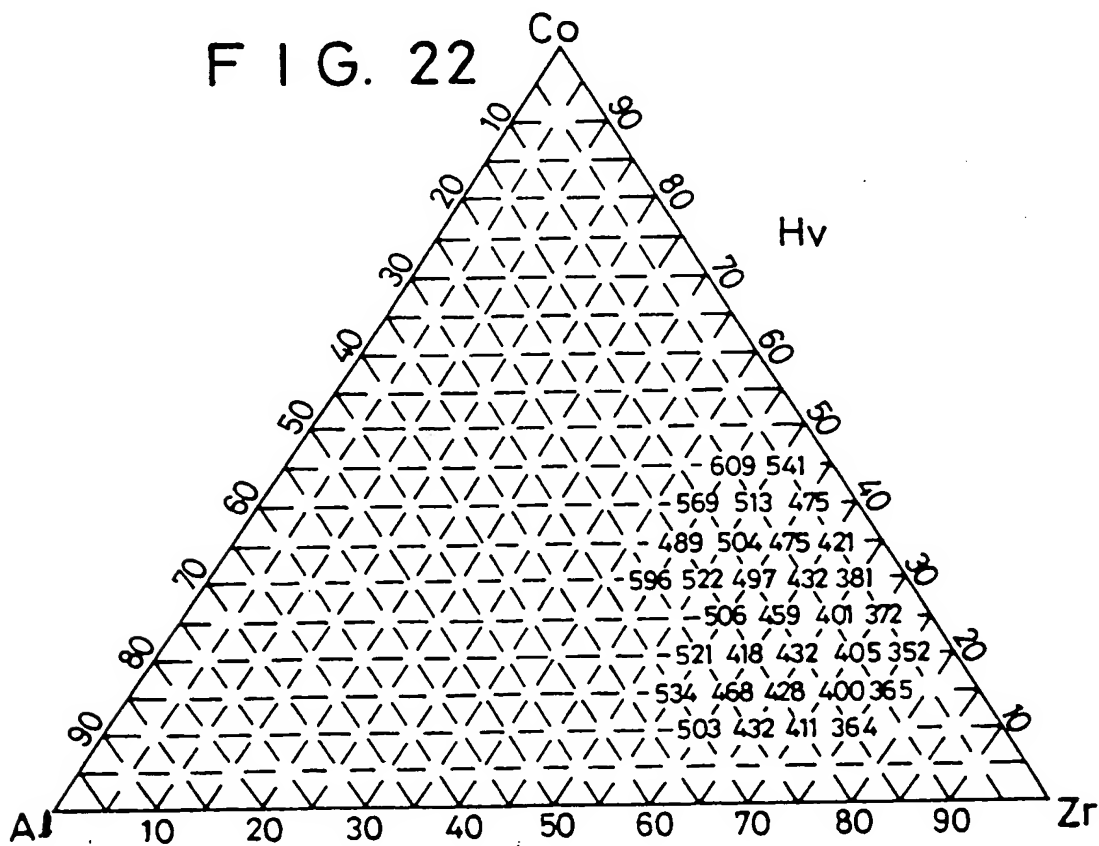


FIG. 22



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 (C07D279/30)-(C07D295/18B1G)-
 [M07C101:06]-

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C07C233/07



⑪ Publication number:

0 433 662 A3

PATENT APPLICATION

⑤ Int. Cl. 5: C07C 233/07, A61K 31/165,
 C07D 295/185, C07D 213/40,
 C07D 211/16, C07D 211/22,
 C07D 233/18, C07C 233/13,
 C07C 233/36, C07C 275/16,
 C07C 237/22

⑩ Priority: 16.11.89 US 437727
 09.10.90 US 594484

④ Date of publication of application:
 26.06.91 Bulletin 91/26

⑤ Designated Contracting States:
 AT BE CH DE DK ES FR GB GR IT LI LU NL SE

⑨ Date of deferred publication of the search report:
 03.07.91 Bulletin 91/27

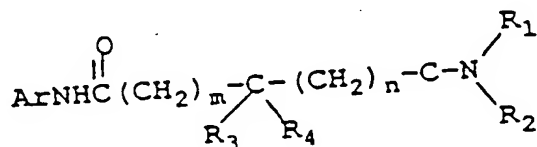
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⑤ Acat inhibitors.

⑦ The invention is novel compounds having acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitory activity of the formula I



(I),

EP 0 433 662 A3

The invention further comprises a process for the preparation of compounds of the formula I, pharmaceutical compositions containing them and the use of compounds (I) for the preparation of pharmaceutical compositions useful for treating hypercholesterolemia and atherosclerosis.



DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	DE-A-3 531 836 (J. AMATO et al.) * Examples 1-15; claims *	1-5,11	C 07 C 233/07 A 61 K 31/165 C 07 D 295/185
X	US-A-3 542 850 (JANSEN et al.) * Example 27; claims 1-4,15 *	1,2,4,5,11	C 07 D 213/40 C 07 D 211/16
X	EP-A-0 119 428 (BAYER) * Examples 7-9; claims *	1-4,9-11	C 07 D 211/22 C 07 C 233/18 C 07 C 233/13
X	NL-A-264 432 (RICHTER GEDEON VEGYESZETI GYAR RT) * Examples; claims *	1-4,11	C 07 C 233/36 C 07 C 275/16 C 07 C 237/22
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 80, 23rd July 1958, pages 3734-3738; S.L. SHAPIRO et al.: "N,N'-polymethylene bis anilines and related compounds" * Page 3736, table III *	1-5	
X	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS I, November 1978, pages 1338-1350; G.V. BOYD et al.: "Synthesis and reactions of cyclic isoimidium salts" * Page 1339, column 2, compounds 6b-6h; page 1345, column 2, lines 10-46 *	1-5	
X	LIEBIGS ANNALEN DER CHEMIE, 20th October 1981, pages 1844-1864; G. HIMBERT et al.: "Synthese und Reaktivität von 3-Aminopropiolamiden" * Page 1860, table 5; compounds 9a,9e; page 1863, lines 9-20 *	1-5	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 C 233/00 C 07 C 237/00 C 07 C 275/00 C 07 D 211/00 C 07 D 279/00 C 07 D 295/00
A	EP-A-0 297 610 (WARNER-LAMBERT) * Whole document *	1-12	

The present search report has been drawn up for all claims

Place of search

Date of completion of search

Examiner

The Hague

22 April 91

HELPS I.M.

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

- E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons
&: member of the same patent family, corresponding document



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Application Number

EP 90 12 1904

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 283 742 (WARNER-LAMBERT) * Whole document *	1-12	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		22 April 91	HELPS I.M.
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